Green College Lectures

The natural environment and disease: an evolutionary perspective

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Einstein defined the environment as "everything that isn't me," and so mankind's natural environment includes not only the physical environment but other organisms. Medical science tells us a great deal about diseases today, but for the evolutionary zoologist an interesting question is how they have interacted with mankind through evolutionary history.

The zoological starting point is that *Homo sapiens* is a primate whose DNA separated from that of its closest living relations, the chimpanzee and gorilla, a mere three million or so years ago—just 100 000 generations. Primates differ from every other major mammalian group in being largely confined to the tropics or subtropics.

The other groups that have many species—for example, the carnivores, the rodents, the two ungulate groups—all have species adapted to temperate, indeed arctic conditions. Thus, to take each of these groups as a whole, they have a wide tolerance of temperature and other environmental conditions. Most primates are restricted in their ranges. The limits of this range are not determined simply by the direct effects of temperature or even climate, but man shares with other primates a sensitivity to low temperatures with comparatively high cold limits and "critical temperatures." Nevertheless, unlike other primates, man has spread to almost all regions of the world, and except in India the most dense populations are not now in the tropics. Archaeological and anthropological evidence suggests that as early man struck out from his tropical habitat he depended on shelter (such as caves and stone huts), on the skins of animals, and on fire for help in maintaining body temperature.

The natural environment that *Homo sapiens* was exposed to in the cradle of its evolution was almost certainly tropical Africa. Although cold was not a problem, there were other environmental pressures. Foremost of these were diseases due to parasites—ranging from viruses to large helminths. Why are such parasitic diseases of man so prevalent in tropical environments? There are two environmental features. Firstly, the abundance and variety of other primates, often living in proximity to man, provide a rich and diverse reservoir of hosts from which parasites may transfer to man; thus there is the opportunity for many zoonoses. Secondly, there are the abundance and variety of insects and other disease vectors. Their variety is a reflection of the faunal richness of tropical environments; their abundance throughout the area arises in part from the climate. In the absence of a winter period breeding may occur throughout the year and the generations are short and overlapping.[1]

Not all parasites of man have been either gained from primates or carried forward from the prehominoid past. Leishmaniasis is shared with rodents and carnivores, plague with rodents, and hydatid disease with dogs, to name but three. But primates do suffer from a great range of diseases: helminthic, protozoal, microbial, and viral. A good example is malaria; there are many different species of *Plasmodium* often specific to particular monkeys or apes, but some may cause infection in other species. Two of the four *Plasmodium* species that affect man (*P vivax* and *P malariae*) may be transmitted to chimpanzees, which have three species of their own—two of these will infect man. Clearly *Plasmodium* and primates constitute a group of parasites and hosts that have interacted in their evolutionary history.[2]

Cross infections between man and primates occur with many other parasites, such as bacterial species in the genera *Leptospira* and *Treponema* and the gut bacteria *Salmonella* and *Shigella*. Although man and different primates may have different habitats—some arboreal, others ground dwelling—disease may be transmitted between them not only by vectors but also at common resources such as waterholes, which are important sources of cross infection by gut parasites such as *Shigella* and *Entamoeba*. Another and modern site of cross infection is the rubbish bin; here transmission is from man to primates—Rolland *et al* isolated antibiotic resistant bacteria from baboons in Kenya.[3] Such transfers may lead to a source of antibiotic resistant bacteria developing in the natural environment.

Perhaps the most important and least understood common pool of parasites concerns the viruses, especially arboviruses, transmitted by arthropods.[4] Yellow fever is an old association; more recently O'nyong-nyong disease has arisen in east Africa, probably as a mutation of chikungunya virus. Other viruses, transmitted through the body fluids, are at present matters of concern. Just 10 years ago Marburg or green monkey disease was recognised; it seemed to be a zoonosis, and transmission in central Africa, where it was sporadic, was believed to cease after four or, at the most, eight generations in man. Monkeys are often hunted, killed, and eaten in this region—probably an ancient primate habit, for chimpanzees will capture and eat young baboons. Scratches, bites, and the mixing of blood or other body fluids is likely in these circumstances. This seems the most likely origin of the "AIDS virus." No doubt such events have occurred in the past, but the biological environment was different and the earlier modified viruses seem to have become some of evolution's casualties. Those who have studied the relation of simian diseases to man have long feared such an event.[5]

Although the effects of such diseases in other primates may be less, this is not always so and panprimate epidemics may occur. In late 1966 Goodall observed an outbreak of a "polio like" disease in the chimpanzees of Gombe. At least a tenth of the population—mostly young or adolescents—were affected, and half of these died. Dr Glenn Hausfater has told me that subsequently in a wide area of east Africa the effects of this disease could be seen as lameness or other muscular disability in baboons, man, and other primates that had been in the young age group in 1966. The agent was probably a Coxsackie virus A.

Undoubtedly the endemic burden of disease on man in tropical environments sapped his vitality. A trypanosome infection, for instance, can use 25 g glucose per hour—that is, a fifth of the blood

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glucose content or about one sixth of the rate of use in a marathon runner, and of course in the disease this use continues for days. It is no wonder that trypanosomiasis was called "sleeping sickness."

Disease also reduced population growth, through mortality and reduced reproduction—an occurrence that continues. Many studies have shown how endemic malaria induces amenorrhoea with the consequent loss of fertility. Mortality due to malaria—in contrast, for example, to that due to most cancers—occurs mostly in those who are not in the reproductive phase of life. Thus the combination of these two factors has had a profound effect on population growth; the elimination of malaria has had the converse effects.

So we may conclude that, notwithstanding the abundant sun and water of the tropical environment and the ease with which fruit and vegetables could be grown and gathered, man was essentially "bogged down" in the environment of his evolutionary home by the burden of diseases—many of simian origin—both zoonoses and those from his prehominoid past.

Movement and its effects

A major change came with the movement of man away from the tropics and subtropics. The date of this event is uncertain, but recent evidence from the mitochondrial DNA of different races suggests that movement from the African tropics was under way about 100 000 years ago.[6] This is about 3500 generations ago—not much in biological terms. The last major spread of man into northern Europe and Asia and across the Bering Strait into the Americas occurred about 10 000 to 15 000 years ago—that is, about 400 generations ago. Man himself had a great impact on the environment of these temperate regions. Many species of large—and hence slow breeding—animals became extinct, possibly as a direct effect of their sudden exposure to a clever hunter who used fire, and could throw spears and fire arrows.

By moving to colder regions beyond the habitat of several of the disease vectors and their animal reservoirs mankind would have left various diseases behind—sleeping sickness, yellow fever, and so on. The original spread was probably in small isolated bands; numbers were depressed perhaps by a shortage of food (in the inclement seasons) and other new stresses, but contagion for disease would have been less. The interplay of vector population size, host population size, and transmission rate on the epidemiology of a disease is well illustrated by some of the models that ecologists have constructed.[7] These show how the transmission of a disease is very susceptible to changes in the numbers, behaviour, and longevity of both host and vector—factors that are heavily influenced by the natural environment.

As mankind spread out from the subtropics probably small groups would break off and migrate away. Joseph Birdsell of the University of California studied such situations in Australian aboriginals and various island people, relating this to evidence about man in the Pleistocene. The groups would consist of perhaps three to seven individuals, but when isolated and in a reasonable environment their numbers would double every generation to reach maxima of 200-300 before further splits occurred. In areas where the environmental conditions caused the numbers of the mosquito or other vector populations to be low, or to have a seasonal period of great rarity, many tropical diseases would "drop out." The small size of population units could reduce transmission of those diseases carried from person to person, and the rate of transmission would be further reduced if the group moved and changed "camp" frequently—faecal material and perhaps sickly infective individuals would be left behind.

This theory is confirmed by several studies of small tribes and communities in environments as varied as those of the Eskimos, the Australian aboriginals, and forest dwellers in Papua or the Amazon. These have shown that only a few diseases afflict each group, and because of demographic stochasticity—that is, the large influence of chance events in small populations and "founder effects" (the infections that happened to be carried by the founders)—these may differ. Data assembled by Black for various Amerindian tribes in the Amazon basin illustrate this pattern,[8] and Eveland *et al* found unique strains of *Escherichia coli* in particular tribes.[9] Strangers who sought to join tribes could be "initiated"—that is, stressed so that symptoms of disease would show. As with many tribal carnivores—for example, mongooses or hunting dogs—perhaps only fit individuals would survive initiation.

Change in biological environment

While the human race was fragmenting and moving to new physical environments during the Pleistocene it was also altering its biological environment. It was domesticating animals: first the dog, then cattle, sheep, and the pig; and, finally, the horse. These animals came to live in close proximity to man, and in place of zoonoses with other primates as the natural host mankind became exposed to infectious agents from these new associates. If the standard list of diseases man shares with animals today is plotted against the length of time each species has been domesticated it can be seen that accumulation of common parasites is related to time.[10] Given the ability of viruses and bacteria to evolve rapidly, it seems quite likely that some other of our diseases may have arisen from this environment at that time, such as smallpox from cowpox.

As man was a tropical animal he took to caves and other shelters in colder regions. Thus unlike most of the apes and some hunter gatherers in subtropical areas, who move around a great deal, once the migration had been completed man became less mobile. Domestic animals were brought into the caves or huts for protection against predators—for example, wolves or human neighbours—and many diseases were transferred. There are even today examples of human infection from animals when there is an unusually close association—for example, people working with sheep may become infected with the tick borne "louping ill" virus.

Besides man and domestic animals there were other animals in this new environment. These were of two types: firstly, those that had initially occupied the caves (principally swifts, swallows, rock doves, and bats) and, secondly, those that were attracted by the debris that accumulated from the activities of man and his animals (principally rats and mice). Both groups of animals had bloodsucking ectoparasites—disease vectors—associated with them. For example, apart from the bed bug (*Cimex lectularius*), all cimicidae are associated with cave dwelling animals (swallows, bats, pigeons), and human bed bugs are similar to the bat bug (*C pipestrelli*). A far more important transfer from bats than the bed bug, whose role as a disease vector is small, is probably the rabies virus: it seems to be almost benign in some bats; perhaps it went into dogs first and finally passed to man, where it is at its most fatal. (Man, of course, brought the dogs into the caves and into contact with the bats.)

Rodents, particularly rats, must have moved in with man many thousands of years ago. From these man gained new ectoparasites—particularly fleas—and hence new disease vectors. Bubonic plague caused by the bacillus *Yersinia pestis* is undoubtedly a disease that spread to man when he moved into desert/steppe like regions—the Black Death (1349-70) was probably one manifestation of this. The sudden onset of such plagues or the maintenance of a disease such as malaria may be understood with the help of models such as those of Anderson and May.[7] There will be no disease at low levels of vector and host populations unless the efficiency of transmission is very high (as with sexually transmitted diseases). But the situation is different when both populations become large—as when cities were formed and, because mankind was living in one place and wearing clothes, there were large individual burdens of ectoparasites. When Thomas à Becket was undressed after his murder at Canterbury in 1170 a contemporary observer recorded that his innermost garments of haircloth seethed with lice, "like water simmering in a cauldron." In this new environment diseases could spread as never before. The Old Testament and historical records from the ancient world all provide ample evidence of plagues—epidemics of some diseases. These were a reflection of the environment at that time. Malaria, which had probably been left behind when man initially left the tropics, could now maintain itself, for human populations were more dense and also, perhaps, man's bad land management had

increased the breeding grounds for mosquitoes and hence their population was also larger. A few hundred years ago in Europe malaria extended as far north as Sweden.[11]

Some, but by no means all, religious and cultural taboos of this period served to reduce the efficiency of transmission. Of greater importance was the improvement in living conditions, such as the elimination of farm animals and vermin from the home. On the other hand, as travel increased from the Middle Ages onwards so did the rate of spread of vectors and diseases; for instance, the bed bug, *C lectularius*, seems to have been first found in Britain around 1500. Most recently the biological environment has been changed again and vector borne diseases have become rare in the non-tropical regions. The advent of DDT and other insecticides some 40 years ago speeded the process, but malaria retreated from northern Europe a century ago; changes in the natural environment, draining of marshes, and so on lowered the number of vectors (mosquitoes), and the pool of infective hosts thereafter became reduced.

In temperate environments insect vector populations build up slowly because their development is slow and their generation time long. Nevertheless, if the climate became warmer the faster generation time might cause large vector populations and the resurgence of some diseases now limited to more tropical environments. Gillette has suggested that through this mechanism the range of various tropical diseases might be widened as one effect of the rise in temperature world wide predicted from the current increase in carbon dioxide levels due to burning fossil fuels.

Diseases due to physical environment

From this glance at the future of parasitic disease let us return to consider those caused by the physical environment alone—in particular, the cancers (though recognising that some are caused by viruses). The earth depends for its energy on radiation, but radiations may damage biological molecules. Three to four hundred million years ago life was just invading land, though it had been luxuriant in the sea for about as long again. As the seawater screens out many of these radiations the early marine organisms were protected from the effects of most extraterrestrial radiations; they evolved and many produced oxygen. As the atmosphere developed the oxygen screened out some of the shorter ultraviolet waves, and the ozone layer the middle ultraviolet range (200-300 nm). I suggest that the delay in the colonisation of the land by life may have been due not solely to problems of biological design (walking, self weight, desiccation, and respiration, on which we biologists concentrate) but also to the high intensity of ultraviolet radiation. Given that life evolved exposed to the present levels of ultraviolet it is not surprising that this source of energy has been used, and some ultraviolet radiation is beneficial for the synthesis of vitamin D. Unless they have a special diet people who largely avoid exposure to the sun will suffer from vitamin D deficiency, leading to rickets and osteomalacia.

Nevertheless, ultraviolet can also damage the DNA of the skin cell, leading to skin cancers: melanomas and those classified as non-melanomas (basal cell and squamous cell carcinomas). Ultraviolet radiation is not the only cause, especially of squamous cell carcinomas, but it is the major cause of melanomas and basal cell carcinomas. Melanin provides protection, and thus the northern white races are particularly susceptible to these skin cancers when exposed to the sun. As with caves and northern lands, this shows the new hazards that man faces when he moves to a new natural environment. For example, those who settled in Australia in the mid-nineteenth century often developed non-melanoma skin cancer—notwithstanding their Victorian modesty and wide brimmed hats. The modern habit of sunbathing, however, increases exposure. The number of cases of the most serious skin cancer—melanoma—doubled in Queensland in the decade to 1977, while higher increases (associated with more sudden exposure) have been recorded in Scandinavia—and a correlation found between the incidence of skin cancer and Mediterranean holidays, when there is a sudden exposure of previously shaded, melanin free areas. As the incidence of non-melanoma cancers rises in later life perhaps the full impact of sunbathing in the swinging '60s is yet to be seen. The natural environment is not benign; mankind changes site and habits at his peril.

Radiations of shorter wavelength are the ionising rays—*x* rays and gamma rays. These, with the α and β rays (atomic particles), are the radiations whose effects arouse most public concern. Radiation may damage DNA; most frequently only one strand of the helix is damaged and this will be repaired. But damaged or incorrectly repaired DNA leads to harmful effects, such as cell death or damaged cells multiplying; the latter may lead to cancer or, in the case of the reproductive cells, to genetic damage to the next generation. All living organisms are sensitive to ionising radiation and those with dividing cell systems especially so; large animals seem more sensitive than small ones. Perhaps because of their low rates of cell division cold blooded animals (reptiles and fish) and adult insects are especially resistant.

Mankind (and other organisms) receive radiation from a variety of sources: cosmic rays from space; gamma rays from terrestrial sources; radon and thoron from materials in the earth, giving α radiation; and internally from radioactive materials in our bodies. Additionally there are artificial sources—now comprising just under 15%. The largest component is due to medical procedures, but this "average effective dose" does not allow for the age at exposure. Most categories are more or less evenly spread through life, but much of the medical exposure may be towards the end of life. Chernobyl has added a small amount of radiation, about 2%.

The natural components of radiation are influenced by environmental factors. After passage through about 400 m of air cosmic rays will have lost 10% of their energy; the same loss will occur in half a metre of water or a fifth of a metre of rock. Thus as we go down into the earth we reduce the cosmic component very quickly, but the terrestrial component (including radon) will increase—maybe very rapidly in certain types of rocks—for example, Cornish tin mines. Of more interest to many is the effect of going up. Air shielding of cosmic rays falls off rapidly, so that when flying in Concorde one gets a larger dose per unit time than in a subsonic plane, but the faster the flight the less the exposure time so that the total dose is less.

What are the disease implications of this facet of the natural environment? From the evolutionary viewpoint there are two important points. Firstly, the normal natural levels of exposure have very small effects in population terms—that is, the risk to man from the average annual natural dose in the United Kingdom is about 1 in 40 000. Secondly, the effects, if any, of these low levels are cancers, and except for leukaemias these mostly manifest themselves after many years. In other words, mortality is mostly postreproductive and so outside the scope of "natural selection." Thus evolutionary biologists would not be surprised if natural radiation caused some disease in later life.

The gas radon constitutes about 30% of the radiation dose in the United Kingdom. There are worldwide variations in the amount of radon in the environment, depending on the underlying rocks. Nevertheless, man's habit of having a home, which is necessary if he is to colonise non-tropical areas, also influences and generally increases exposure to radon, as his home prevents the escape and dilution of the gas. Modern designs for heat conservation do this by reducing the ventilation; thus even today man is still modifying and changing his interaction with the natural environment.

To summarise the conclusions from this Odyssey through the history of the human species, its environment and diseases, they are: (1) the natural environment is not benign: it is a patchwork of quilt of dangers and opportunities, a sort of gigantic "snakes and ladders" board; (2) mankind evolved in the tropics, probably tropical Africa, spreading from this rich but pestilential Garden of Eden. It was necessary to create our own microenvironment—living in caves and wearing clothes—which brought us in contact with new diseases and new vectors; (3) man has uniquely spread over the earth; he has left his Garden of Eden, his "ladder." New opportunities have been taken, but these have led to new disasters and new challenges—for example, solving the problem of cold, with caves, houses, and clothes, led to rabies and bed bugs; solving the problem of the meat supply through domestication of animals led to

smallpox, helminthic disease, and possibly tuberculosis; solving the problem of food storage and advancing civilisation through occupational specialism led to a settled way of life, to towns and cities, and so to plagues. Today, 10 000 years later, enjoyment of sunshine may lead to skin cancer, heat conservation in homes to accumulation of radon and lung cancer, and widespread travel, personal contact, and tolerance between people of all races to the escape of a virus—that causing the acquired immune deficiency syndrome—whose peculiar features would have doomed it to extinction 10 000 years ago.

The fourth and final conclusion is that the diseases that have arisen in these new natural environments that man has encountered have all in time been much reduced in importance. Sometimes this has been by the discovery of a cure, but more often it has been by modifying our mode of life by changing the way we interact with the environment—by preventive medicine.

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Medicolegal

Failure to warn

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The House of Lords decision in Sidaway *v* Bethlem Royal Hospital has not marked the end of the debate over informed consent.[1] Two recent Court of Appeal cases have clarified further the extent of the doctor's duty to inform a patient of the risks of a proposed medical or surgical procedure. In both cases health authorities were found negligent in the High Court for failing to provide sufficient information. But doctors will no doubt be reassured by the fact that in each case the decision was reversed unanimously by the Court of Appeal.

The Sidaway case established that a doctor's duty of care in giving advice or in informing a patient about the risks of a procedure or treatment is the same as in making a diagnosis or carrying out treatment. The test for deciding whether a doctor has failed in his duty of care in any of these spheres—has been negligent, in other words—was laid down in Bolam *v* Friern Hospital Management Committee, in which it was emphasised that "a doctor is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that art"[2] (though two of the law lords in Sidaway asserted a judicial right to override medical practice not to disclose a particular risk when disclosure was obviously necessary for the patient to make an informed choice.)

The two recent cases turned on two points left open by Sidaway. In the first, Blyth *v* Bloomsbury Health Authority, decided in February, the issue was: does the duty of disclosure differ where the patient expressly asks questions?[3] The point at issue in the second (Gold *v* Haringey Health Authority, decided last week) was: does the doctor's duty differ if the context is non-therapeutic rather than therapeutic? Is the doctor obliged to give fuller information about failure rates and other options if the operation is for contraceptive rather than therapeutic purposes? In both the Court of Appeal firmly declared that the Bolam test applied. If a responsible body of his colleagues would have given no more information at the time the doctor will not be held negligent.

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Communication failure?

The Blyth case concerned an injection of Depo-Provera administered at University College Hospital in 1978. Mrs Blyth, a qualified nurse, sued over alleged side effects of the drug, given as a contraceptive after vaccination against rubella. She complained that she was not sufficiently informed about the possible side effects, and that if she had been better informed she would not have taken the drug. She blamed several different side effects on the drug but the judge rejected the claims, apart from bleeding and menstrual irregularity.

In the Court of Appeal Lord Justice Kerr said that all three appeal judges had difficulty in following the findings on which the judge, Mr Justice Leonard, had based his conclusion that there was negligence, and also on what aspects of the evidence he had based those findings. The judge did not accept Mrs Blyth's evidence that she had asked several specific questions, but found that it was more probable than not that she had asked for some information and advice and that she had expressed some sort of reservation about Depo-Provera and made some form of request for reassurances about it. He did not find any individual negligent but said: "I conclude that the defendants were negligent in not advising the plaintiff as fully as they ought to have done, in the light of her manifest and reasonable request to be advised. I make it clear that I am not criticising any individual. The evidence does not enable me to say where the fault occurred but merely to conclude that it occurred somewhere. Most probably it was simply a failure of communication." He accepted the evidence of the senior house officer who spoke to Mrs Blyth that she would have left the patient with the impression that there were no serious side effects other than irregular bleeding. But one of the other doctors in the department kept a file on reported side effects of Depo-Provera as part of her own research, which included a range of other side effects that had been described in a small number of cases, and the judge thought that "the full picture" should have been made available to Mrs Blyth as she sought information and was a qualified nurse. He awarded damages of £3500.