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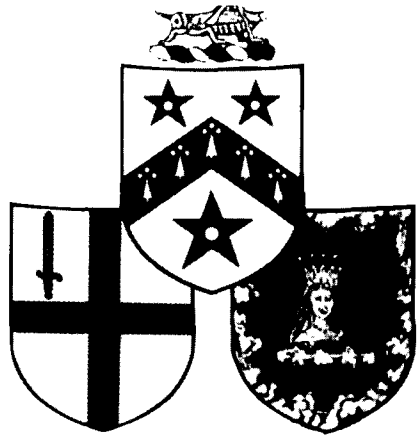

TROPICAL DISEASES

Three lectures given by

PROFESSOR FRANCIS COX PhD DSc
Gresham Professor of Physic
(and the other biological sciences)

FIRST SERIES

1 Their Problem or Ours?	**13 October 1992**
2 The Uninvited Guests	**20 October 1992**
3 Malaria: The Battle We Cannot Win	**27 October 1992**

GRESHAM COLLEGE

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Gresham College, Barnard's Inn Hall, Holborn, London EC1N 2HH
Tel: 0171 831 0575 Fax: 0171 831 5208
e-mail: enquiries@gresham.ac.uk

Tropical Diseases: Their Problem or Ours?

The title of my talk tonight is in the form of a question and, in order to answer it, it is first necessary to establish the nature of the problem, to determine its causes and to look for possible solutions. To start with, we need look back no further than the fifteenth and sixteenth centuries and the time of Thomas Gresham. This followed the most exciting period of human exploration and was characterised by the establishment of trade routes that brought spices and silks, gold and ivory, wood and coal across the oceans that had until that time divided up the world. However, goods were not the only things that spread around the world, with trade came people, both freemen and slaves, and with people came disease.

Nobody knows for certain when infectious diseases first afflicted humans but if we reflect on our evolutionary past it is clear that mankind must always have harboured parasitic organisms of various kinds. When we lived in small, scattered groups, infectious diseases posed no problems as a considerable degree of contact is required to ensure effective transmission. However, as the groups became larger the opportunities for the spread of diseases increased but diseases still remained localised until the establishment of trade routes, and the large ports necessary to sustain them, opened up the possibilities of worldwide epidemics. The origins of many infections can be traced to particular geographic areas, for example malaria spread from Africa, cholera from India and syphilis from Europe. Gradually many diseases became distributed worldwide but with the discovery of the nature of microbes and the subsequent development of vaccines and drugs coupled with the availability of clean drinking water it was possible that the twentieth century would see the eradication of all such diseases. Indeed, spectacular progress has been made; the killer disease, smallpox no longer exists and measles, tuberculosis and poliomyelitis are no longer major health hazards in the developed countries of the world.

In the tropics, however, things are different and most infectious diseases are today concentrated in developing countries mainly in Africa, India, South East Asia and South America. In many parts of Africa, for example, the situation is no different from what it was a century ago and in some places it is distinctly worse. In these lectures, I shall concentrate on the hard core

of diseases that can now be regarded as "tropical diseases". In this lecture, I am going to discuss nature and magnitude of the problem and how it affects both the people living in developing countries and us, and in subsequent lectures I shall try to show how modern transport and travel can bring tropical diseases to all of us and then I shall deal in detail with what is probably the most important infectious disease in the world, malaria. In the next series of lectures, I shall continue this theme by discussing the part that the pharmaceutical industry could play in the control of tropical diseases and what the constraints are, the ways in which tropical diseases, though their effects on various conflicts, have shaped the present political map of the world and, finally, show how improvements in the control of animal diseases could contribute to human health.

In order to put tropical diseases into perspective it is necessary to start with some facts. The impact of any disease can be measured in terms of mortality and morbidity. Mortality is a crude but easily measured statistic but morbidity, the amount of illness, is less easy to quantify but is much more important. There is a world of difference between someone who, for example, is suffering from a simple malaria fever, and someone who is comatose with complicated malaria, yet both would be recorded as a single attack. Dead people, particularly children, represent individual tragedies but chronically sick people who cannot work but have to be maintained can place an intolerable burden on the rest of the community. However, we only have figures for the numbers infected and the numbers dying but these do serve to indicate the magnitude of the problem. The current world population is about 5.3 billion of which about three quarters live in the developing world. About 85% of all children are born in these areas and about 97% of infant mortality, mainly from diarrhoea, respiratory diseases, measles and malaria, occurs there.

The global prevalence of the major infectious diseases can be best illustrated by reference to the table below. The important thing about figures such as these is that they do illustrate the size of the problem but hide the fact that most of those infected live in the developing world. Also hidden is the fact that deaths from diarrhoeal infections and measles are preventable.

Disease	Number infected (000)	Mortality (000)
Respiratory diseases	15,000,000	10,000
Diarrhoea	3,000,000	4,300
Measles	67,000	2,000
Malaria	350,000	1,500
Bilharzia	250,000	250
Amoebiasis	500,000	70
Hookworm	800,000	50
HIV	10,000	?
[AIDS]	[350]	?

[Source: World Health Organization various documents]

However, the most important tropical diseases are those that occur nowhere else and which cannot be easily prevented and, In 1975, the World Health Organization targeted six diseases for special attention and, to the surprise of many people, these included the following

Disease (Vector)	Number infected (000)	Mortality (000)
Malaria (mosquitoes)	350,000	1,500
Bilharzia (snails)	250,000	250
Filariasis (insects)	90,000	<1
River blindness (flies)	17,000	<1
Chagas disease (bugs)	17,000	60
Leishmaniasis (flies)	12,000	<1
Leprosy	12,000	<1

[Source: World Health Organization]

There are two important points about this list. Firstly, with the exception of leprosy, all these diseases have life-cycles that involve a vector,

something which does not apply to the major diseases of the developed world, which adds another dimension to any control programme. Secondly, these vector-transmitted diseases are caused by organisms that are parasites, technically protozoans and worms, whose cells are highly evolved and similar to ours, and which have developed ways not only of surviving in two quite different hosts but also of evading the immune responses in both hosts. This means that it is difficult to design safe and effective drugs or vaccines and the ability to evade the immune response results in long chronic debilitating infections in those that survive. Although, with the exception of malaria, the mortality is comparatively low the morbidity is high thus these diseases place an intolerable burden on the resources of the countries affected.

Having established that there is a problem, the next question is how to solve it. The various periods of colonisation brought to the developing world a number of advances including the assumption that Western medicine was appropriate for tropical countries and that the drugs and vaccines that had been so successful in Europe and North America would also be the answer to the problems of the developing world and that the insecticides developed for agricultural use would eradicate the various insect vectors. Unfortunately, this has not been the case. Western medicine is expensive and requires an elaborate infrastructure of doctors, hospitals and an educated population. In addition, the reliance on drugs to cure infections and vaccines to prevent them presupposes that effective drugs, vaccines and insecticides are available (or will become available) and diverts attention away from more traditional methods of prevention and, in particular, vector control. The current worry is that too many scientists, politicians, sociologists and the Press are raising false hopes and that the technological advances being made in the developed world will not after all be transferable, or even applicable, to the developing countries.

How can tropical diseases be controlled? In theory, vector-borne diseases can be attacked at the vector stage thus breaking the life cycle, infections can be prevented by vaccination and infections can be cured with drugs. In practice this is not as simple as it seems and all such control schemes are beset with problems. Let us consider vector control. There is no doubt that the use of insecticides has changed the face of agriculture. Crude insecticides, such as arsenic, first used in the United States have been

replaced by highly effective and specific compounds the best known of which are DDT and Dieldrin. Both were extremely effective and DDT was used with great success until the 1970s to control the mosquito vectors of malaria. Then two things happened: insects developed resistance to insecticides and environmental damage became widespread. The tragedy is that the anti-mosquito insecticide spraying campaigns, which also had an effect on the sandfly vectors of leishmaniasis and the bugs that transmit Chagas disease, did not contribute to the spread of resistance. What caused the problem was the use of DDT and Dieldrin for agricultural purposes. As farmers became more dependent on insecticides, resistance began to develop and this required the application of more and more insecticide. Unfortunately, the excess washed off and ran into the waterways feeding the pools and streams where the mosquito larvae developed. Here, subjected to increasing levels of insecticide, resistance was selected for with the result that by the beginning of the 1980s resistance was world-wide. Now, these insecticides are no longer being manufactured and have been replaced by less toxic ones which are, however, more expensive. With the removal of selection pressure, it is likely that the mosquito vectors would be susceptible to carefully controlled attack but the insecticides are no longer available. It is difficult to attribute blame. Third world farmers felt that they were entitled to the seeming benefits of insecticides and had to use them to compete in international markets and developed world manufacturers felt that they had to penetrate the potentially immense market afforded by the third world. In the event both sides must share the responsibility for the present situation and both are now suffering the consequences.

There is, however, some reason for optimism. The newer insecticides, although more expensive, are more powerful, more selective and less environmentally damaging and one of the effects of the higher prices is the realisation that it is necessary to employ more efficient methods of application. It is too late to do anything about the problems already created but not too late to learn from the mistakes made.

The use of drugs has also passed through similar phases. The original drugs used for everyday infections in the developed world were crude and often dangerous but the discovery of penicillin and the development of other antibiotics has made it possible to cure a vast range of potentially life-

threatening conditions. Spectacular progress has been achieved with the virtual elimination of such diseases as tuberculosis throughout much of the world and river blindness is now being successfully treated at reasonable cost and with great success largely through the intervention of one pharmaceutical company working in collaboration with the World Health Organization. Leprosy can now be treated easily with combination of new and old drugs (multidrug therapy) and the World Health Organization is confident that the prevalence of this disease can be reduced to 1 in 10 000 in susceptible populations and eliminated altogether in the next century. Unfortunately, resistance to many drugs has now developed and strains of pathogens resistant to a range of antibiotics present a continual problem especially in hospitals. In the developed world, there is a plentiful supply of antibiotics and a number of alternatives are always available wherever resistance is encountered. In the developing world, the situation is different. Antibiotics are not easily available and those that are put a heavy financial burden on overstretched health budgets. There is, therefore, an understandable tendency to use too little of a particular drug, the discontinue use too soon and for mothers to share the precious drug between several children, all conditions that generate and maintain drug-resistance. However, this is not the main problem. For some of the major tropical diseases, there are no safe and effective drugs at all and some of those in use are over fifty years old. For leishmaniasis, the drugs used are potentially dangerous, cannot be given by mouth and must be injected 3-4 times a week for 25 weeks or more. For Chagas disease the drugs can be given orally but treatment must be continued daily for 90 days. For sleeping sickness, treatment requires several courses of 30 or more daily injections and the treatment itself is fatal in 1-5% of patients treated.

The impact of drug resistance is best illustrated by reference to malaria, the first disease for which a specific drug was used. Quinine, already in use when these Gresham Chairs were established and well documented since 1600, has been the mainstay of antimalarial treatment ever since and is still, for many, the drug of choice. There is no shortage of potentially antimalarial drugs and several hundred have been developed over the years. However, the number now available has shrunk to a mere four or five as each has become associated with adverse side effects. Chloroquine is the drug most widely used but its efficacy has been declining because of increased drug resistance all over the malarious world. As with pesticides and antibiotics, resistance is favoured

by the use of too little of the drug and incomplete periods of treatment resulting in the gradual selection of forms of the parasite that can survive ever increasing levels of the drug. However, resistance to chloroquine is not as simple as this and it seems that resistance arose as single mutation in the Far East and gradually spread to India, South America and Africa to such an extent that this drug is hardly effective along the east coast of Kenya, one of the great holiday resorts of the world. Resistance to another drug, pyrimethamine, is continually arising spontaneously in all parts of the world and resistance to halofantrine, first registered in 1988, has already been reported. I shall discuss this subject further in my third lecture and all I intend to do here is to state the problem and to try to apportion blame. Immediate responsibility must lie with the misuse of these drugs but, as about half of all "prescriptions" come from unofficial sources this problem cannot be solved. Blame must also be apportioned to those working in various public health schemes for too much reliance on a "quick cure" approach instead of tackling the underlying problem of eradicating the cause of the disease. This can be considered as another case of the misapplication of Western medicine to a tropical problem. It has also been suggested that the pharmaceutical industry has not done enough to develop cheap and effective drugs and I shall consider this topic in my next series of lectures.

It is less than a century since Louis Pasteur developed the first vaccines and changed the face of preventative medicine for ever. Single injections early in life can protect against most major killer diseases and currently over two thirds of the world's children are being vaccinated against poliomyelitis, tuberculosis, measles, diphtheria, tetanus and whooping cough. However, these vaccines are not yet reaching all those who require them and it is estimated that over the lives of over 3 million children could be saved if this could be achieved. There are, unfortunately, also a number of bacterial and viral diseases for which no vaccines are available although there is no reason why they should not be developed apart from the fact that they are unlikely to have any commercial value. The World Health Organization estimates that such vaccines could save the lives of over 8 million children. There is no doubt that vaccination is effective but it is expensive. It costs between $10-15 to protect a child against the common diseases of childhood, a total cost of $1.5 billion most of which has to be met by the developing countries themselves. Health does not come cheap.

In addition to the bacterial and viral diseases against which the development of vaccines is largely routine, there are the parasitic infections against which there are no vaccines and few prospects of any. The possibilities of developing vaccines against these parasites, with their complex organization and the possession of numerous ways of evading the immune response, present major challenges to research workers, particularly molecular biologists, and a vast amount of effort is being devoted to this aspect of immunology. Malaria is a good example. At least one billion dollars has already been spent on the search for a vaccine with very little real success despite overcoming the numerous problems posed by the peculiarities of the parasite. I shall be discussing this further in my third lecture. Bilharzia is another disease targeted for a possible vaccine but, again, the vast amount of money spent has produced few tangible results. For both of these diseases, the limited, but encouraging, successes can be used to justify some degree of optimism but for sleeping sickness and Chagas disease the possibility of any vaccine looks bleak. The African trypanosomes that cause sleeping sickness are able to switch their antigens so frequently and unpredictably that they would be able to counteract any vaccine and in Chagas disease the pathology is actually caused by the immune system reacting with host cells so a vaccine would be counterproductive.

So far, I have tried to establish that there is a problem and that, although we do have some solutions, these may be beyond the grasp of those in need. What are required are remedies that are cheap, effective and with benefits immediately apparent to all those involved. The application of Western medicine and advanced technology is not the solution. New pesticides, drugs and vaccines will be expensive to produce and deliver and it is unlikely that major drug companies will be willing to devote the time and money necessary to products that produce little return. However, what can be done is to return to more conventional methods of disease control and the more effective use of pesticides, drugs and vaccines already available. The precedent is the control, over the last century, of many of the common diseases of more temperate climates by education and the application of what can be termed low technology solutions. Better housing, for example, discourages the bugs that transmit Chagas disease, careful disposal of faeces away from water used by women and children reduces the incidence of bilharzia and the use of bednets impregnated with insecticides is very effective at reducing malaria. This

last example is an excellent one. Mosquitoes rest after feeding and will rest on curtains or bednets. It takes only a minute amount of insecticide to impregnate a bednet, which only needs to be done annually, and this is therefore cheap, effective and causes no environmental damage. The immediate impact can be seen in a reduction of mosquitoes thus the householders can see that their efforts are being rewarded. Other solutions include the introduction of mosquito-feeding fish into streams and ponds providing both a method of malaria control and additional food.

Why is it important to us that tropical diseases should be controlled? Putting aside humanitarian considerations, the developed world cannot continue to support the developing world. Over the next decades, the population of the developing world will increase while that of the developed world will decline. The advanced countries are already suffering from the debts owed by less developed countries and the developing world will eventually have to become self-sustaining and even a net exporter of food and goods if its economies are to survive and are robust enough to withstand natural catastrophes such as droughts and floods On a minor, but nevertheless significant scale, tourism is an excellent source of foreign currency. Self-sufficiency and safe conditions for tourists can only be achieved if the tropics are not handicapped by their indigenous tropical diseases and stable economies will permit the development of pesticides, drugs and vaccines for local use. The unspoken danger is that with improved health more children will be born and all the benefits achieved will be wiped out by problems of overpopulation. Here education is all important and it is to be hoped that with declining infant mortality the desire for large numbers of children will decline as has happened in the developed countries and in populations held in check by Governments as in China. The hard lessons to be learned are that the future of the developing countries lies in their own hands and that Western science and medicine must not offer false hopes of any easy solution. In addition, tropical diseases present an ever increasing direct threat to us and I shall discuss this in the next lecture.

Tropical Diseases: The Uninvited Guests

In my last lecture, I talked about a number of diseases that are now regarded as tropical diseases and the tropics and subtropics are where the majority of human diseases began. When people lived in villages, the infectious diseases they contracted were probably mostly acquired from the animals they hunted. Diseases common to humans and animals are known as zoonoses and a number of zoonotic infections exist today. Rabies, which occurs in a number of wild carnivores is a good example of a disease that is transmitted directly to humans but there are many more some of which occasionally hit the headlines, brucellosis from cattle is one and toxoplasmosis, acquired from cats, is another. Other diseases are transmitted through insects that feed on both humans and wild animals and examples include plague in rats and fleas, and yellow fever in monkeys and mosquitoes. Gradually the distribution of diseases that we see today began to be established when, over 6000 years ago, humans first began to live in large groups thus facilitating the ready transmission of disease from one to another and gradually many of the wild animals originally involved dropped out of the cycle. Today, many of the infectious diseases we see are specific to humans and human behaviour has been instrumental in determining the present pattern of disease. Diseases that were distributed worldwide have now have been pushed back to their heartlands and diseases that helped to shape the present political map of the world still render the poorer parts of the world even poorer.

To a certain extent we can cope with our endemic diseases. In the United Kingdom we regularly experience influenza and colds yet these are not normally serious diseases. In other parts of the world, they are. On the other hand, malaria is a life-threatening condition for us whereas most people in the tropics experience several attacks a year with little discomfort. This is because with endemic diseases we receive antibodies from our mothers and these see us over the first few dangerous years. Exotic diseases, whether they pass from individuals in the developed world to the undeveloped or <u>vice versa</u> present novel problems. Such diseases have never been welcome guests but today, with our health-conscious societies, we should be more aware of exotic diseases than ever before but this does not seem to be the case. Travellers die from malaria, food handlers pass on cholera and a "can't happen to me" attitude has contributed to the spread of AIDS. In this lecture, I

am going to talk about lessons from the past, why we cannot afford to live in ignorance, why we cannot let up on our vigilance and finally I shall discuss some difficult ethical problems.

The original scattered and isolated patterns of infectious diseases began to be mixed up with the movements of populations and the establishment of trade routes. Hippocrates, in his "Airs, Waters and Places" in the fifth century BC recognised diseases of travel as a specific category of infection. We can learn much from one of the earliest documented examples, the "plague of Athens" in the fifth century BC. Nobody knows for certain what this disease was but what is known is that it apparently arose in Africa, crossed Asia and arrived at Piraeus by ship and, over a period of four years, killed a third of the Athenian army and thousands of civilians and eventually contributed to the defeat of the Athenians by the Spartans. In the second century BC, smallpox accompanied the Roman army from Mesopotamia and ravaged the Roman empire. In the Middle Ages, plague spread from Mongolia and China, along the trade routes and from port to port until the whole of Asia, Europe and North Africa was involved, further spread in Africa being limited by the Sahara Desert and the sparse populations. After the discovery of the New World, syphilis arrived from Europe with the Spaniards and malaria and yellow fever with the slaves. These two diseases are transmitted by mosquitoes and, as local species were susceptible, quickly became endemic, yellow fever subsequently disrupting the building of the Panama Canal and malaria causing considerable mortality and morbidity in South America. In this century the virus causing AIDS, which originated in Africa, has been an unwelcome guest in many countries.

Of all these diseases, plague is probably the best documented and most feared but it is from this disease that we have learned most lessons. Quarantine, and the creation of a cordon sanitaire was pioneered in the tiny Derbyshire village of Eyam. Plague arrived from London in fleas (although this was not known at the time) in a batch of used cloth and spread from the house of the tailor to neighbouring houses and from them to adjoining properties. The local clergyman persuaded the villages to stay in the plague-ridden village and to avoid contact with anyone else lest they spread the disease to surrounding areas. The majority of the villagers died but the disease was contained. The last pandemic of plague occurred at the end of the last

century beginning in Canton in China and spreading via the ocean trade routes all over the world including Australia. There, in Sydney, the spread of the disease was meticulously traced from the dockside to nearby houses and thereafter from house to house. Plague, therefore, illustrates two important public health points, the need to isolate the disease and the ability to trace a disease back to its source. Today plague continues to exist in populations of wild animals but is no longer even a minor health problem, smallpox has been eradicated and syphilis is easily cured thus three of the most feared diseases of the past have virtually disappeared. However, we cannot afford to be complacent because other diseases are already waiting in the wings and nowadays the dangers come mainly from the tropics.

The slow spread of diseases along the trade routes is also a thing of the past. We are no longer an isolated island, nearly two million of us visit the tropics each year, Jumbo jets can convey 400 or more passengers across the world in less than a day, it is possible to fly from London to Africa and back again within 24 hours and battalions of troops can be transported from one continent to another within a matter of hours. Travel is now so commonplace that we tend to approach a holiday in Ghana in the same way as a weekend in Paris but, for some, a sojourn abroad will tragically turn out to be a Trojan horse, for the tropics are full of diseases easily transported elsewhere.

For convenience, the problems of imported diseases can be divided into three groups, diseases in imported animals, diseases acquired by travellers or service personnel while out of this country and diseases carried by immigrants.

The only serious disease likely to be imported with an animal is rabies. Rabies is a viral disease endemic in many parts of the world with very few exceptions of which the British Isles is one. The virus is maintained in wild animals, particularly foxes in Europe, but the dog is the most usual source of human infections. Rabies is a very dangerous disease and it is seldom realised that, despite heroic medical intervention, it is invariably fatal once the first symptoms appear. The British Isles have stringent anti-rabies precautions yet there are numerous attempts to smuggle dogs and cats into these islands. Such actions are totally irresponsible as we have no way of controlling the disease once established other than the wholesale slaughter

of wildlife. The British attitude to rabies typifies our approach to other imported diseases and suggests that it is we, and not the peoples of the developing world, that require education.

The second problem area is the acquisition of infectious diseases by travellers, particularly the more adventurous ones. Every day, several hundred passengers board flights to tropical Africa believing that the most dangerous part of the trip is the journey itself. In fact, the danger does not begin until they have landed because every one of them has put themselves at risk of contracting a potentially fatal disease. Most, of course, reduce this risk by taking suitable precautions but, nevertheless, the risk is there. Many bacteria and viruses contaminate food and drink and most travellers are now aware that they should not drink unsterilized water or eat salads or other uncooked food. Few intestinal infections are fatal yet the fear of the almost immediate consequences of unwise eating or drinking reinforces the need for caution. Other diseases that are much more dangerous do not present the same immediacy and tend to be treated more casually.

Malaria is a potential killer yet several thousand travellers acquire this disease by neglecting simple precautions. According to the World Health Organization, 30 million people visit malarious areas every year and between 0.2 and 2% of these become infected with a fatality rate of between 0.5 and 9%. This represents at least 300 and at most over 50 000 unnecessary deaths, statistics that must be taken seriously. In the British context, this translates into about 2500 recorded imported cases each year and about 6-12 deaths. Infection can be prevented in several ways. The best way is to avoid being bitten by mosquitoes by using a combination of insect repellents, long sleeved shirts and trousers and keeping away from places known to be frequented by mosquitoes particularly in the evenings Mosquito nets coupled with insecticide spraying will protect sleepers and should always be used in malarious areas. Antimalarial drugs can be used prophylactically and, although not as effective as they used to be because of the spread of resistance, do provide a considerable degree of protection as can be seen in the table below:

EFFICACY OF VARIOUS PROPHYLACTIC DRUGS AGAINST MALARIA

Treatment	Efficacy %
None	0
Chloroquine (low dose)	29
Chloroquine (high dose)	53
Chloroquine/Proguanil	76
Mefloquine	93
Fansidar	84

Modified from Parasitology Today, 8, pp. 61-66: 1992

For the British traveller, the chances of dying from malaria are 20 times greater in those taking no drugs than in those who take some form of prophylaxis. For anyone travelling to the tropics, it is essential to seek informed medical advice because different drug combinations are recommended for different areas. The Malaria Reference Laboratory at the London School of Hygiene and Tropical Medicine provides an excellent information service but few travel agents give any warning about the dangers of malaria and many general practitioners are insufficiently aware of the complexity of the problem so as to be able to give informed advice. In general, in areas where there is no chloroquine resistance, chloroquine plus proguanil are the drugs of choice and in areas where resistance occurs, mefloquine should be used. Fansidar, a combination of pyrimethamine and sulfadoxine, is no longer recommended. No drug, as can be seen from the table above, is completely safe and effective and particular individuals such as children and pregnant women need special advice. Many cases of imported malaria occur because the full course of treatment is not followed. Those who do become infected, or think that they might be infected, should seek immediate medical help because the most severe form of the disease, malignant tertian malaria, can cause cerebral damage and be fatal in a matter of hours for children or days for adults. Once the infection is becomes established, the patient may die despite massive treatment regimens. It essential to seek early medical advice and is surprising how many people returning from the tropics with fevers do not mention the fact that they have been abroad to their doctor as a delay of a few days in beginning treatment may prove fatal. Symptoms of malaria may appear as long as six months after exposure and many people will not associate

their holiday a long time ago with their present symptoms. To the inexperienced, the early symptoms of malaria, mainly fever, headache, myalgia and malaise, resemble influenza so the greatest danger occurs when symptoms of a disease acquired, say in September, appear in the middle of an influenza epidemic in January. Most general practitioners never see a case of malaria and can therefore be forgiven for not making a diagnosis if the patient has not alerted them to the fact that they have been abroad. In the hands of experts, the diagnosis of malaria is quick and simple and treatment usually immediately successful. The tragedies occur when the patient and the doctors settle for paracetamol instead of chloroquine.

Imported malaria is not confined to travellers. Malaria was endemic in Europe well into this century and can still, theoretically, be transmitted by our indigenous mosquitoes. Living near an airport can also be dangerous as in 1989 five Swiss citizens living near Geneva airport were infected by the bites of mosquitoes transported in an aircraft from a malarious area. In Britain, we have had mini epidemics following the two world wars and, more recently, during hot summers. The sources of infection have been various, returning service personnel, retired colonial civil servants, young VSO workers and immigrants. Relatively few people die from malaria but those that recover can harbour the infection for many years, the malignant form for about five years and the more benign forms for sixty years or more. Such individuals can act as sources of infection in damp areas during long warm summers and, like the traveller, they should seek treatment for as long as they are infected they remain a danger both to others and themselves.

I have dwelt on the subject of malaria partly because it illustrates a number of important principles and partly because it is one of the best known of the imported diseases. However there are a number of others, some rare and some, unfortunately, increasingly common. The possibility of acquiring a tropical disease rarely seen in this country is well illustrated by reference to the experience of 143 young people who visited Cameroon as part of Operation Raleigh. Only 85 bothered to take part in a medical follow-up and, of these, 22 were infected with the worm that causes river blindness and one showed the first signs of eye damage. Fortunately, river blindness is easily treated but what will happen to the twenty or so who are presumably infected and have not sought medical advice? Another infection easily acquired is

bilharzia, or schistosomiasis, a disease caused by a worm that develops in freshwater snails and which bores through the skin to reach the blood vessels of the intestine or bladder. This is one of the great diseases of antiquity and one recognised and recorded in detail by the ancient Egyptians. This is a very difficult condition to diagnose as the symptoms may take years to develop and the best method of prevention is to avoid contact with snail infested water especially in Egypt. Both these examples illustrate the ease with which tropical diseases can be acquired, the difficulties in diagnosing the condition afterwards and a general lack of understanding of the problem.

So far, I have considered tropical diseases that can be acquired by individuals but pose no real threat to the population to which they return. However, there are some diseases that do present a threat to the community as a whole. One of these is tuberculosis. Tuberculosis, which so frightened our Victorian ancestors, is still a major disease which affects about 1.7 billion people, about a third of the world's population, and kills about 3 million mostly in the developing world.

GLOBAL PREVALENCE OF TUBERCULOSIS

Region	Infections (millions)	Deaths
Western Pacific	574	894 000
South East Asia	426	932 000
Industrialised	382	42 000
Africa	171	656 000
Latin America	117	220 000
Mediterranean	52	163 000
TOTAL	1722	2 907 000

[Source: World Health Organization]

However, as these figures show, tuberculosis is not confined to developing countries and the real problem is that, after decades of decline, it is now once again increasing. The decline in tuberculosis in Britain has been spectacular. In the early 1940s over 23 000 people died from this disease

every year and, until recently, cases have been relatively few. The decline has been partly due to improved living conditions but mainly due to vaccination with BCG and the relative ease with which early infections can be cured. The first warnings of increases in the numbers of cases of tuberculosis came from the United States but over the past year or so the numbers in the United Kingdom have increased from just over 5000 in 1987 to 5500 in 1990 and an estimated 5750 in 1992. One specialist London hospital now sees 50 cases a month. Where do these cases come from? Tuberculosis is largely a disease of the poor and elderly and also ethnic minorities and migrants. It is easily passed from one individual to another and, therefore, rapidly spreads in crowded and unhygienic conditions. Most of the tuberculosis in Britain comes in with immigrants and refugees and despite rigorous health checks some infected individuals slip through the net. Illegal immigrants present the greatest health risk as their entry goes unrecorded as do their movements and contacts. Unfortunately, once established, tuberculosis can easily spread and everyone from the youngest to the oldest and from the weakest to the fittest is at risk. Vaccination is the best protection against tuberculosis yet some District Health Authorities intend to discontinue routine vaccination. In some districts, where only the babies from ethnic minority groups have been vaccinated, the authorities have had to abandon or modify their procedures because of perceived racism. The balance between health, finance and upsetting people's feelings is in danger of getting out of hand. Vaccination is cheap and effective, drug treatment is relatively expensive and has to be continued for 6-12 months and death is irreversible. Ours are small and overcrowded islands ideal for the spread of diseases such as tuberculosis and we must decide where our priorities lie before it is too late.

It may be too late already. The last unwelcome guest I wish to introduce is the human immunodeficiency virus, HIV, and the disease it causes, Acquired Immunodeficiency Syndrome, AIDS. It seems pointless to argue about where and how this infection arose, to most scientists it is clear that it must have arisen in African monkeys or apes and been transmitted to humans, probably by eating these animals, and subsequently spread around the world as a sexually transmitted disease. Whatever the origins, there is no doubt that HIV is not only a devastating infection in Africa but is also the most important imported disease ever encountered by the developed world. In 1985, about half of all

cases occurred in the developing world, particularly in Africa, and this figure has now risen to about 70% and is expected to rise to 90% by the year 2010 representing a massive reservoir of infections with the potential to establish in developed countries. Worldwide, AIDS is essentially a heterosexual disease, 90% of all cases being transmitted through male-female sexual intercourse according to the World Health Organization, but, in Britain, is still largely confined to the homosexual and drug-using sections of the community although there is evidence that it is now passing into the heterosexual community. However, this may not indicate a dramatic change in the spread of this disease as it is now clear that the majority of cases of heterosexual AIDS can be traced to immigrants, visitors or travellers from Africa. This is the time to stop this disease entering the indigenous heterosexual population though active educational campaigns, such as those that have been so successful in Switzerland, and possibly by imposing restrictions on those entering the country as is practised in Australia. There is no really effective drug against AIDS and little chance of a vaccine so preventative methods are the only ones available.

There is another reason why it is essential to curb both tuberculosis and AIDS and this is because these two infections are synergistic. Patients with AIDS are immunodepressed and more likely to suffer recrudescences of latent tuberculosis infections and in those with tuberculosis, the progression from infection with the HIV organism to AIDS is more rapid.

In this lecture I have tried to show that we are not isolated from the diseases of the tropics and that we are all at risk although at present, this risk is low. However, there are dangers inherent in pretending that the dangers do not exist and we must try to ensure that everyone is educated to these risks. The responsibility lies with all of us, travel agents and tour operators must be made to accept the need to warn travellers of the dangers they face, general practitioners must be made more aware of exotic diseases, travellers must look after their own health before, during and after their trips, immediate financial savings must not be made at the cost of future epidemics and the sensibilities of the few must not be allowed to threaten the health of the many.

Tropical Diseases: Malaria The Battle We Cannot Win

In my first lecture I discussed the problems posed by tropical diseases and their impact on the developing world and in my second lecture I drew attention to the fact that many of these diseases are not as remote from us as we might like to think. Of necessity, my discussion has had to be rather superficial and general but tonight I am going to talk in some detail about one disease, malaria. I have selected this disease partly because of its importance, partly because it illustrates the ways in which medical research progresses through a series of triumphs and setbacks and partly because this is the disease on which I have worked for the whole of my research career. I should also like to take this opportunity to introduce you to some of the ways in which the concepts of modern molecular biology are being applied to the problems raised by one very important infection as an illustration of the wider potential of such applications.

Of all the tropical diseases, malaria is the best known and the most feared and has attracted more attention from scientists and clinicians than any other disease. However, despite all this attention, and uniquely among all the infectious diseases, malaria is a greater threat than it was a century ago and all the hopes of eradicating it which were so high only a quarter of a century ago have been dashed one by one. Gradually new battle lines have been drawn up, we have retreated from eradication to control and from control to containment and now, as more and more difficulties arise and the costs of each new advance soar, the whole of the international anti-malarial campaign is at risk as a new disease with a higher profile, AIDS, takes centre stage.

The story of malaria is a fascinating one and one in which the various skeins have been woven into a tapestry so complex that no single person is capable of comprehending either the parts or the whole. The most recent comprehensive textbook on malaria ("Malaria: Principles and Practice of Malariology" edited by Walther Wernsdorfer and Sir Ian McGregor and published by Churchill Livingstone) contains nearly 2000 pages and this merely touches the tip of the iceberg. This said, the story of our understanding of malaria has been told many times but it is a story well worth the retelling and one that sets the scene for our discussions this evening.

For over a million years, humans have been exposed to malaria which our ancestors acquired from the apes and monkeys in Africa and spread beyond that continent as mankind expanded its horizons. The disease was well known to the ancient Greeks and Homer wrote about the fevers that occurred mainly in the summer and autumn. Its association with marshes was also recognised in the fifth century BC when Empedocles, a student of Pythagoras, cleared the marshes around the city of Selinus in Sicily and thus protected it from malaria, an event commemorated on a gold coin. Hippocrates, in the fourth century BC in his "Airs, Waters and Places" classified the forms of malaria into groups that we recognise today. Malaria plagued the Roman Empire, Julius Caesar almost certainly had malaria, in the words of Shakespeare "he had the fever while he was in Spain", it disrupted the crusades, created the "white man's grave" in West Africa and, having been transported to the New World, caused havoc during the creation of the Panama Canal. In my next series of lectures I shall have more to say about malaria and its effects on wars and empires and all I want to do here is to point out that the disease, many of its pathological features and its association with marshes were known for centuries before the end of the nineteenth century when the scientific study of malaria began in earnest.

The end of the nineteenth century was a magical period for medical research and many of the great discoveries concerning the nature and causes of infectious diseases followed Pasteur's discovery of bacteria. This too was a golden age of malariology. What was known at that time was that malaria caused fevers, comas and death and that it could be cured with an extract from the bark of the Cinchona tree (now known to contain quinine) and there was considerable speculation about its cause. The most widely held belief was that it was air-borne and caused by some kind of poison, probably arising from the marshes, and, after the discovery of bacteria by Pasteur, it was suggested that bacteria in the mud caused the disease, an altogether tenable suggestion that influenced contemporary thinking. However, this was not the case and in 1880 a French doctor, Alphonse Laveran, found organisms in the blood of a patient in Algiers. Over the next few years several advances were made by Italian scientists who discovered that the parasites lived in red blood cells in which they multiplied and were all released simultaneously every 48 or 72 hours, depending on the species involved, causing the periodic fevers characteristic of malaria. During this period it also became clear that the

causative organisms were not bacteria but were protozoans, complex single celled organisms, with bizarre life cycles. Still nobody knew how the parasites were transmitted and the discovery that they required a mosquito in which to complete their life cycle was made through a combination of the intuition of Patrick Manson and the laboratory expertise of Ronald Ross towards the end of the decade. Thus the life cycle involved parasites that were injected into the human host and multiplied in the blood to produce about 16 daughter individuals that caused fevers as they were released. At some point during the infection, sexual stages were produced and these were taken up by a mosquito when it fed, fertilization occurred in the gut of the mosquito and, after another phase of multiplication, infective stages were produced and, when the mosquito fed again, these were injected into the human host to complete the cycle.

There was, however, one piece missing from the jigsaw. There was always a delay of about a week after the mosquito fed before the parasites appeared in the blood and nobody had seen the forms injected by the mosquito enter a red blood cell. Where did the parasites go during this time? It was nearly fifty years before this question was answered when Professors Shortt and Garnham, working at the London School of Tropical Medicine, discovered that the injected parasites underwent a massive phase of multiplication in the liver before entering the blood. Thus the whole life cycle had taken nearly seventy years to unravel but there were to be no more major discoveries to be made although details are still being worked out today.

These discoveries provided the basis for the rational control of malaria. Essentially this involved attacking the mosquitoes by draining swamps and removing other sites where the female could lay her eggs by using insecticides such as Paris green (a copper-arsenic mixture). Later, DDT, invented in the 1930s and synthetic insecticides such as Dieldrin, introduced in 1940, were used to kill the adult insects in and around the houses. Infected people could be cured with quinine or chloroquine, which was developed in the 1930s, and infections could be prevented by taking drugs such as paludrine. By the 1950s, the stage was set for the eradication of malaria and the old enemy began to collapse, first in Italy then Ceylon (now Sri Lanka), Venezuela and Greece. By 1956, malaria had been virtually eradicated from Europe, North America, the Middle East, Chile, Venezuela and Ceylon and the World Health

Organization adopted its policy for the elimination of malaria throughout the world. Ten years later this ideal had to be abandoned and today there is as much malaria as there was a century ago, the number of people infected is increasing and we have no weapons left to defeat it.

What went wrong? Firstly mosquitoes became resistant to DDT. This occurred largely because of its use in agriculture and the overspill of the insecticide into water where the mosquitoes bred. This led to the gradual selection of resistant mosquitoes however this was also accompanied by the emergence of mutant mosquitoes that were totally resistant and these quickly occupied the habitats occupied by the less resistant forms. Resistance to DDT is a recessive trait and its spread is therefore relatively slow but resistance to dieldrin is dominant so once established spreads very quickly. Resistance to insecticides is complex, in some forms it involves the detoxification of the compound while in others the uptake of the insecticide is inhibited, sometimes it involves one gene and sometimes several thus it is difficult to implicate any single mechanism of resistance. The final problem is that resistance to one insecticide brings with it resistance to another, a phenomenon known as cross-resistance. The problems of cross-resistance coupled with environmental damage caused by insecticides such as DDT and dieldrin has led to their being withdrawn from manufacture. The net result is that insecticide resistance in mosquitoes is now world wide and, even where it is not a serious problem, the developing world has no access to the cheap and effective insecticides that once made the eradication of malaria a real possibility.

There are, of course, new insecticides but many of these are expensive and resistance has already developed to most of them. Stringent regulations now govern the manufacture and use of all kinds of pesticides and there is very little likelihood of any cheap and safe insecticide becoming available in the immediate future. Meanwhile, insecticides continue to be used on a small scale, for the treatment of bednets for example, but this is unlikely to contribute to the eradication of malaria.

There are two other ways of combatting malaria, chemotherapy and vaccination, and research in both of these areas is being pursued with vigour. In order to understand what is being done and why it is being done it is necessary to say something about the biology of the malaria parasite itself. Malaria

parasites are single celled organisms belonging to the animal kingdom and thus their cell organization is complex and comparable with our own. We know a great deal about the biochemistry and molecular biology of these parasites and the functions of many of their genes have been determined and their positions on the chromosomes have been mapped. Unfortunately there is an additional complication and this is that the various stages in the life cycle differ biochemically and antigenically from one another. The details of the life cycle are complex but can be summarised as follows:

SUMMARY OF MALARIA LIFE CYCLE

Stage	Mosquito	Human
Sporozoite	Salivary glands	Blood vessel
Exoerythrocytic multiplication		Liver
Erythrocytic multiplication		Red blood cells
Male and female sexual stages		Red blood cells
Zygote	Gut	
Sporogonic multiplication	Gut	
Sporozoite	Salivary glands	Blood vessel

The problem here is that the malaria parasite does not represent just one form, as do organisms such as bacteria, but six distinct stages, each occupying its own specific site and differing from others. As the life cycle progresses, the parasite presents a moving target and the challenge is to find ways of attacking each stage before it can transform into the next.

It is against this background that one must consider the use of drugs bearing in mind the fact that the drug must be effective against a particular parasite biochemical pathway without damaging the comparable host molecules. There are several drugs in our armoury but none is completely effective nor entirely safe and resistance has developed to all of them. In order to understand the problem it is necessary to say something about the way drugs are developed and how antimalarial drugs work. There are two ways of developing specific drugs, the rational way, in which a key molecule or biochemical activity of

the pathogen is identified and a drug designed to attack it directly, and the empirical way in which numerous compounds are tested in the hope of some effect and the target identified subsequently. All the antimalarial drugs currently available have been developed on an empirical basis but we do know how most of them work. We know most about chloroquine, a drug developed in the 1930s effective against the dangerous erythrocytic stages and the mainstay of antimalarial treatment and protection should the parasite develop as far as the liver stage.

Malaria parasites live inside red blood cells where they feed on the haemoglobin by breaking it down into a globin component which they use and an iron-containing component which is toxic. The parasites detoxify this iron component using an enzyme which converts it into a harmless form. Chloroquine works by inactivating this enzyme thus the parasite is killed by a toxic iron compound which it has itself created. However resistance to chloroquine is now widespread. Chloroquine resistance was first noticed in the Far East and South America in the 1960s and has since spread throughout the world. Unlike insecticide resistance, where the acquisition of resistance has been slow and associated with exposure to small quantities of the pesticide, it seems as if a single mutation can change susceptibility to chloroquine to resistance in one step and it appears that this has occurred only one or twice yet this has been sufficient to make chloroquine ineffective throughout the world.

Pyrimethamine is another excellent antimalarial drug which works by inhibiting a parasite enzyme known as dihydrofolate reductase but resistance against this drug has also developed. Resistance to pyrimethamine arises from one of three mutations and has arisen spontaneously on many occasions but these mutations are cumulative and the presence of all three renders the parasite very resistant indeed. The malaria parasites also possess one or more genes for multiple drug resistance, such genes also occur in tumour cells and are responsible for pumping a drug out of a cell before it can do any damage.

Malaria parasites, therefore, have evolved many ways of developing resistance to antimalarial drugs and this is so effective that resistance to the most recently released drug, mefloquine, has already been reported. There is one further problem and this is that when infected blood is taken up by a mosquito the sexual stages of different strains of parasites can cross-fertilize.

Thus if an individual infected with both chloroquine-resistant and pyrimethamine-resistant parasites the resultant progeny in the mosquito will contain a proportion of parasites resistant to both drugs and these will be passed on to another individual when the mosquito feeds again. There are now many examples of combined resistance to chloroquine, pyrimethamine and other drugs.

There are now very few safe and effective antimalarial drugs. There is resistance to chloroquine, pyrimethamine and quinine; mefloquine is expensive and potentially toxic and halofantrine, which has just been introduced, is expensive, very variable in its activity and should be reserved for the treatment of cases resistant to all other drugs. There is great hope for a Chinese herbal remedy, qinghaosu, but it seems that it may be no better than quinine and resistance to it has already developed. Apart from this, there is only one new drug in the pipeline and as it takes at least ten years to develop any new drug, and if one is developed the parasite will almost certainly become resistant, the outlook for malaria chemotherapy looks very bleak. This is not due to any lack of effort, 250 000 compounds have been tested over a twelve year period, it simply reflects the fact that the malaria parasite is a very formidable enemy indeed.

Vaccines are essential components of any control scheme and essential for eradication. There is no doubt that vaccines are effective, they have been instrumental in the eradication of smallpox and the virtual elimination of measles, poliomyelitis and tuberculosis from much of the industrialised world. A vaccine against malaria is therefore a holy grail and the World Health Organization has made this a priority. No single biomedical project has received so much attention and thousands of scientists and billions of dollars have been dedicated to this project so far with little success.

The difficulties involved in developing a vaccine against malaria are immense. There are three problems to be overcome, the complexity of the life cycle, the numbers of antigens expressed by each stage in the life cycle and the ability of the parasites to evade the immune response. Antigens are the molecules that elicit and are recognised by the immune system and in, for example, virus infections, these remain unchanged during the course of an infection. In the malaria parasite, the various stages in the life cycle are antigenically

different so in order to prevent infection it would be necessary to develop a vaccine against the sporozoites injected by the mosquito. However, these remain in the blood for only a few minutes before entering the liver where the dividing parasite begins to express a new repertoire of antigens requiring a different kind of vaccine. Should a single parasite survive in the liver it could give rise to 10 000 progeny with the potential of producing vast numbers of erythrocytic forms once again with novel sets of antigens. Finally, the sexual stages also express a unique repertoire of antigens. The second problem is the nature of the parasite itself. Unlike viruses which possess only a few surface antigens, often only two or three, which can easily be identified and used as vaccines, malaria parasites possess hundreds and it has been extremely difficult to determine which of these is protective and which the parasite has evolved to enable it to evade the immune response.

There is also little agreement about which stage a vaccine should be developed against. The problems can be best explained by reference to what is currently the most favoured candidate antigen, the protein that coats the sporozoite. The sporozoite is an ideal target for immune attack because if a vaccine against this stage was effective it could prevent infection altogether. The molecular structure of the sporozoite is known in some detail and it is covered with a single protein consisting mainly of repeated sequences of four amino acids. Theoretically, this should form the basis of an ideal vaccine The sporozoite surface protein has been produced in various synthetic forms and expressed in bacteria using the techniques of genetic engineering and used as an experimental vaccine with tantalisingly little success. Theoretically, such a vaccine should have been very effective but now scientists believe that the repeats of amino acids may be used by the parasite as a smoke screen to divert the immune response away from a more vulnerable target. There is another twist to this story and this is that field workers have known for some time that there is no correlation between antibodies to the sporozoite antigen and protection. Nevertheless, the search for a sporozoite antigen goes on.

Other potential vaccines have been developed in the same way and with similar disappointing results. Antigens from the liver, blood and sexual stages have been identified, produced synthetically or by genetic engineering, used as vaccines and have achieved partial or no protection. Interestingly, all the

important antigens so far identified possess long repeats of a limited number of amino acids and the suspicion must be that these cannot be involved in protection and might well be involved in counter protection. An additional problem is that malaria parasites can undergo antigenic variation so a vaccine might not always be protective and might even select for forms that were resistant.

There is one sign of hope for the development of a vaccine and this is the use of a synthetic molecule, based on a number of malaria parasite antigens, developed by a Columbian biochemist, Manuel Patarroyo. This vaccine has now been given to over 30 000 individuals but unfortunately the design of the trials does not permit the evaluation of its efficacy which is said to be over 80% This vaccine is now being field tested, under controlled conditions, in Africa under the auspices of the World Health Organization but it will be many years before its potential use can be evaluated.

While the search for a vaccine goes on, other malariologists have devoted their attention to the ways in which malaria parasites are killed and unfortunately some of these killing mechanisms also cause damage to the host. Reluctantly, many now feel that immunity to malaria is a damage limitation exercise in which the host must suffer some degree of infection and possible pathological damage in order to mount, over a number of years, an immune response which keeps the infection under control. The development of a vaccine under such circumstances is likely to be a very difficult exercise indeed.

There is one further problem. Even if there was a vaccine which was cheap and effective, mathematical models have shown that it would be necessary to vaccinate over 99% of the population in endemic areas to eradicate the disease. This degree of vaccination has never been possible.

I have painted a grim but realistic picture of the chances of controlling or eradicating malaria but I do have some solutions to the problem and here I return to my first lecture. It will have to be accepted that here will be no quick-fix solution, there is no vaccine around the corner and there are no new drugs in the pipeline. Those who insist that, given the resources, the solution will be found are probably more interested in their own research

grants than the welfare of those suffering from this terrible disease. The immediate solution must be a revival of awareness of this disease and a will to take action locally by removing sites where mosquitoes breed, the use of insecticide impregnated bednets and the careful and controlled use of the drugs we have. This will not eradicate malaria but it should improve the lives of millions of people. Even if we cannot win this battle we cannot afford to surrender unconditionally.