THE ROCK CARLING FELLOWSHIP

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The abolition of infection

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The Rock Carling Fellowship
was founded as an annual memorial
to the late Sir Ernest Rock Carling,
for many years a Governing Trustee
of the Nuffield Provincial Hospitals Trust
and Chairman of the Trust's Medical
Advisory Committee

Each holder of the fellowship
will seek to review in a monograph
the state of knowledge and activity
in one of the fields in which Sir Ernest
had been particularly interested and which
is within the purposes of the Trust.
The arrangements provide that the
monograph will be introduced by a
public lecture to be given at
a recognized medical teaching centre
in the United Kingdom

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I

Introduction

It has been put to me that a monograph like this is more interesting if the reader can start by finding out something about the author. One feels a natural reluctance to agree to this but there are reasons for doing so. For one thing, opinions and ideas are not arrived at in the abstract, but as a result of experience, teaching, and one's intellectual environment. As a result a reader who is interested in the validity of ideas will be able to correct or discount them because he knows a little of the history and background of the one who is putting them forward, and those who are interested in methods of training and the development of scientific ideas may find this section worth reading for their own reasons. For those who are not interested on either of these counts it would be best for them to go straight to the next chapter.

While a schoolboy I read books on biological science as well as animal stories but only studied formally the 'hard' sciences, chemistry, physics, and mathematics. I turned to medicine as a career and as a way of life that was worthwhile, because its purpose was to help people. This is often doubted as a genuine motive among students but was, I believe, real in my own case. On the other hand I had a schoolboy delight in the various and marvellous things in the world of nature and of man's invention and this has stayed with me and I am glad not to have grown up to lose the sense of wonder. Now I come to think of it some of my favourite books were entitled 'Wonder Book of . . .', and I have had the same sort of enjoyment in later life from finding new organisms and a little of how they work as I recall feeling when reading those books. Nevertheless, motivation is often a complex thing and I think I have been driven also by a wish to help others in a personal or medical sense. It can be difficult to sustain this when one is lead later, as I was, into scientific work at the bench which although it was directed to solving basic problems could not be immediately applied to medical diagnosis or

care—yet I felt at those times that the science would eventually lead to better ways of 'helping' people, and this encouraged me to keep on. This probably also drives many science graduates working on projects which are part of a programme of medical research.

Although the war was at an intense stage and I went straight into the Medical School at Sheffield I was able to spend one year in an Honours Physiology Course. The teaching and practical resources were limited and I was ill much of the time, but I was able to read classic papers in the subject and struggled to repeat experiments for myself, experiments such as the separation and assay of secretin. Thus I learned to tackle the literature and realized the importance of technical expertise in doing effective research. I returned to general clinical training but was stimulated by the offer of, I think, £15 for a Woodcock Prize Essay to write two essays on the basis of reading the literature; one was on endotoxins, which was rejected as being of too low a standard. I know that the examiners, one of whom was Professor Wilson Smith, had serious doubts as to whether they should turn down the only essay offered, but I was told that they thought it was important to maintain high standards—'It's not good enough as an essay, but it would make a good basis for an essay', I was told—and I learned the lesson that a comprehensive summary of a subject is not enough. A couple of years later the Prize was offered in Physiology so I composed an essay on 'The Role of the Hypothalamus in the Phenomena of Sleep' and this time was awarded the prize —I presume I had learned. I was also fortunate to have a great deal of clinical experience as the classes were small, there were plenty of patients and senior students were often given clinical responsibility. We were, of course, taught with lectures, often given by very senior and experienced teachers, but more than I realized at the time I learned the practical skills of diagnosis and treatment and an understanding of disease by experience at the bedside and from the example of seeing physicians at work.

On graduating it was clear that returning ex-servicemen were likely to get all the training posts for an aspiring consultant physician, so I decided I would like to do rural general practice or academic medicine. Even in my first year as a house officer, I was

involved in research and was, I realize, very fortunate in that the newly arrived Professor Stuart-Harris, on whose firm I worked, told me how to do the clinical side of a study of influenza and pneumonia and therefore educated me in how to make thorough well-planned clinical records, how to collect the right specimens, and how to record the right details. I remember I also had excited discussions with Alick Isaacs about the experiments he was doing on viruses in the tiny virus research laboratory that Stuart-Harris had set up, partitioned off an old hospital ward. Isaacs had come down from Glasgow to learn how to do laboratory work on influenza viruses. I know that once we discussed what virus interference was all about—ideas which were to occupy both of us on many occasions in later years—though at the time what filled our minds was what the latest experiments might mean and how he could do a better or more informative experiment to follow. When I had taken the MRCP I was offered a post as a Research Registrar and I was glad to accept. I wanted a salary to get married on—an important motive! I could continue some clinical work in a diabetic clinic and I was attracted by the chance of learning to work with viruses, under the guidance of Stuart-Harris; of course, I had to put up with the jibes of my contemporaries who said that with virological tests one could say that a patient had influenza one week after he got better and two weeks after a clinician had made the diagnosis! But there's sometimes an advantage in not being too impressed by what others say and what is the fashion. Indeed, although I enjoy the idea of being involved in research in a large field in which there are lots of new things happening and plenty of excitement, I really prefer not to be under the pressure of feeling that someone else has probably done my latest experiment somewhere else. Better to tackle an important question which is not all that popular or competitive and to stay with it and work out an answer, if necessary over a period of years. However, as a young man one needs to get results and acceptance relatively quickly.

I was fortunate to be rejected for military service on the grounds of the residue of my earlier eye lesion and I was also very fortunate to get a post at the Rockefeller Institute in New York City which I held in the end for three years. It was of Assistant in the

Institute and of Assistant Physician in the Hospital. There I had excellent guidance on how to plan and conduct a systematic laboratory study, mostly using influenza viruses, but I also met and heard lectures from great scientists in the Nobel Laureate class. I got the feeling of what top science sounds and feels like, and of the way in which a basic biological question can be asked and answered by critical experiments done in the appropriate biological system and using a range of the best techniques available; I also absorbed a Rockefeller theme that one should try to understand disease and clinical phenomena at the molecular level.

When I left Sheffield no-one was thinking about polio vaccine or viruses grown primarily in tissue cultures, yet when I returned three years later I was so prepared and trained that I could quickly get to work on such topics—an example both of how quickly and unexpectedly science and medicine can change and of the importance of good fortune in preparing one for the future in one's career. In the Virus Research Laboratory, set in a few rooms of a disused nurses' residence at the old fever hospital for the Sheffield area I learned about setting up and running a lab and supervizing and working with staff. Things went well, we did work on the first British killed poliovirus vaccine, recognized a 'new' enterovirus and the disease it caused, studied some 'new' respiratory viruses and then I was strongly urged to go to the Medical Research Council's Common Cold Unit at Salisbury—I was on the External Scientific Staff and they were entitled to move me.

I moved and had to adjust immediately to doing experiments on the biggest and most precious and expensive experimental animal I had ever used, human volunteers, and to learn to tolerate difficult, slow, and frustrating work. I was fortunate also to have at first Sir Christopher Andrewes as the Head of Division. He looked at viruses and infection with the eye of a natural historian. He could comment on the changes in the plants and trees that one saw coming down in the train from London and how they reflected the different soils—pines and heather on the sand of Surrey had disappeared when you reached the chalk downs. He talked with enthusiasm of how the rabbits and the virus were changing as myxomatosis became established on the farms of Australia and Britain. So I began to think more of how the disease that followed

virus infection reflected the genetics and the state of immunity of the individual exposed to infection. I was encouraged in this by Sir Christopher's challenge to think out why some volunteers we infected did *not* have colds and whether it was 'useful' or not for its survival that the virus produced symptoms. This perspective has widened in recent years and in a later section I shall refer to the way in which all the biology of the host and the whole ecology of the viruses and other organisms may bear on whether disease occurs and what sort it is.

It was at this period that I was introduced to some wider matters. For instance, I had to begin to think about the ethics of experimenting on fellow human beings. I was struck by the paradox that the volunteers came to us as fellow human beings and we had a responsibility to treat them as such and make sure they came to no harm. Yet we had to abstract from the experiments we did observations that would stand up to the same sort of rigorous analysis that I had learned to apply at the Rockefeller Institute. I recall visiting my old chief Frank Horsfall Jr in New York about the time of my move. 'Remember', he said, 'that for scientific purposes one human is worth no more than one mouse'—a vivid way of presenting a truth which can only be expressed as a paradox. I also discovered the pleasures of international travel, of talking to someone on the other side of the world who was close to you in mind and with whom you felt kinship because you were tackling the same problem. It was a good feature of the people and the research at that time that we regarded ourselves as a kind of international club, with the WHO as a friendly organizer; we had members in many countries and particularly in the National Institutes for Health in the USA and very fortunately we were not afflicted with the ill-will, rivalries, and suspicion which are, it seems, very much a part of some branches of science. We were, of course, rivals, but we were also friends who would send each other key reagents and plan studies together when this was worth doing. I was, nevertheless, aware that I wanted to remain a doctor and although most of my time was spent in scientific work, I was fortunately able to work one day a week in Medical Outpatients at the Salisbury General Infirmary. However, my central preoccupation was with dimly understood viruses, and the sort of

cells and conditions they required to grow in the laboratory. My 'gut' reaction might be to do something about infectious diseases in the clinic, and especially in developing countries but my rational self said that the most fundamental need was a precise knowledge of the infectious agents and of the specific means of preventing or treating the infections.

Then came next a period of my life which enlarged my understanding in other ways. While still at Salisbury in the early 1960s I was involved in planning the Clinical Research Centre, which finally opened closely integrated with the Northwick Park District General Hospital at Harrow in north-west London in stages spread out from 1970–5. The idea was, as John Squire the first Director expressed it, to 'blur the edges' between the two institutions and to involve each in the other's workings. The CRC was to be a multi-disciplinary biomedical research institute whose divisions reflected both the expertise and interests of the person in charge and also, whenever possible, an aspect of the work of the hospital. The idea was that out of this close contact questions and investigations to answer them would be formulated. Thus there was a Division of Communicable Disease and I and my colleagues took part in the general medical and infectious disease services of the hospital—indeed we helped to set them up. Thus I learned at first hand of the thankless task of planning new buildings—and also that it takes years to fill them and build up the body of people and their working systems which is the 'real' research institute—just as the Church is a body of people and not the building they occupy. But in time the experiment began to work. Some studies were planned ahead, arising from ideas with which we came to the CRC. For instance, David Taylor-Robinson had already worked on the biology of ureaplasmas and it was quite clear that they might be important in causing certain sexually transmitted diseases, and so he worked very hard to set up studies which established their aetiological importance in man, and he also studied the pathogenesis of the infection in tissues cultured in the laboratory and in experimentally infected animals. On other occasions we began with an unexpected clinical observation. For instance, we observed that many children had diarrhoea and vomiting but no bacterial pathogens were found—these illnesses

occurred in the early months of the year and had more respiratory symptoms and certain other clinical features than bacterial cases occurring later. It turned out that we were really recognizing gastroenteritis due to rotaviruses, and we looked systematically for a range of viruses in such cases. During this study a young girl was investigated whose faeces contained a toxin which was picked up because it destroyed the tissue cultures we were using to test for the presence of viruses. We did not just discard the result as a 'toxic' faeces but asked why it was and whether it meant anything. The initial reaction of the journal to which the report was submitted was that this was unimportant, but it has subsequently emerged that the toxin of *Clostridium difficile* was killing the cells in culture and that the organism is the cause of the serious condition pseudomembraneous colitis and other diarrhoeas often associated with the use of antibiotics.[1] This represents a new kind of intestinal disease to be seen in man in Western countries and as we unravel how taking antibiotics may allow the clostridium to grow we are likely to learn a great deal about how the bacterial composition of the bowel is regulated in normal subjects.

Similarly a casual laboratory observation (J. Parry) showed that a common respiratory virus might be detected in the blood of a child who had just been admitted with a febrile convulsion. This suggested that such viruses might disseminate more than is generally realized in children with this syndrome, and this was indeed confirmed. It is possible that such a virus sometimes produces a small focus of infection in the brain and thus causes at least some such fits.[2]

Because the CRC looks after a number of children with immunodeficiency states we were asked to help with a number suffering from X-linked hypogammaglobulinaemia. These children are almost unable to make antibodies, but can be kept well in early life by regular injection of normal human globulin. However, they may get unpleasant infections later on and it turned out that mycoplasmas sometimes cause septic arthritis which they never

1. Larson, H. E., Price, A. B., Honour, P., and Borriello, S. P. '*Clostridium difficile* and the aetiology of pseudomembraneous colitis', *Lancet*, 1 (1978) p. 1063.

2. Lewis, H. M., Parry, J. V., Parry, R. P., Sanderson, P. J., Tyrrell, D. A. J., and Valman, H. B. 'Role of viruses in febrile convulsions', *Archives of Diseases in Childhood*, 54 (1979) p. 339.

do in normal subjects[1] and that enteroviruses cause a syndrome of myositis, dermatitis, and a progressive low grade encephalitis from which they often die, though some benefit is apparently given by administering large doses of immunoglobulin.

We recently studied one of the major problems for pediatricians and general practitioners, the child with frequent and troublesome acute respiratory infections. Dr Isaacs showed, in a carefully controlled study, that such children really exist and are not just reported as troubled by over-anxious parents. They seem to be suffering from infections with common viruses, and not bacteria as some thought; they were not immunodeficient but 4 (out of 16) were found to be unable to make interferon (IFN α) and may well be the first individuals to be found with a genetically determined deficit in the production of IFN α.[2]

All these lines of work were stimulated by recognizing a clinical problem and trying to solve it and the investigations have lead to observations which have increased our understanding both of the clinical situation and the underlying biology.

While getting what stimulus and help we could from clinical work at the CRC we continued on various systematic studies, for instance evaluating our live and killed vaccines in volunteers at the Common Cold Unit and elsewhere and trying to exploit as effectively as possible the new human cell culture derived rabies vaccine—though the initial stimulus for this was the fact that the staff in the animal house did not want to suffer the effects of the previous duck embryo vaccine. Work on cold viruses showed that vaccines were unlikely to be available for such a wide range of serotypes of organisms so we maintained a continued interest in the possible use of antiviral drugs. This all seemed very speculative and unlikely to succeed, but there were two very interesting strands in the work. One was that I had worked on some early antiviral benzimidazole derivatives in New York and this was a good intellectual preparation for these later studies. Of course, we

1. Taylor-Robinson, D., Gumpel, J. M., Hill, A., and Swannell, A. J. 'Isolation of *Mycoplasma pneumoniae* from the synovial fluid of a hypogammaglobulinaemic patient in a survey of patients with inflammatory polyarthritis', *Annals of Rheumatic Diseases*, 37 (1978) p. 180.

2. Isaacs, D., Clarke, J. R., Tyrrell, D. A. J., Webster, A. D. B., and Valman, H. B. 'Deficient production of leucocyte interferon (interferon α) *in vitro* and *in vivo* in children with recurrent respiratory tract infections', *Lancet*, 2 (1981) p. 950.

felt we should work on possible treatments of colds once we had found some causes, but we were not chemists or toxicologists and did not have the resources for the early stages of evaluating potential drugs. However, a number of pharmaceutical laboratories were working in this field who had the knowledge and resources needed, but who did not have the resources for testing candidate drugs in man. We had the necessary facilities and skills at the Unit and so there was a natural partnership or symbiosis, which was expressed by the arrangement that the company usually paid one half of the expenses of the trials and the Council paid the other half. The other strand of the work was my continued interest in interferons. It has been recounted elsewhere how the observations of Isaacs and Lindenmann lead to the discovery of a family of natural antiviral substances, which have many other effects as well, inhibiting cell growth and modulating immune responses. However, right from the beginning in the late 1950s we thought we might use them as antivirals in preventing or treating human disease. We now realize that we could not make enough by the early techniques to affect anything but very localized infections. A series of studies supported by a group of commercial laboratories and the MRC lead to us trying increasingly potent interferon against virus infections of animals or man. They began in the 1960s and were mostly unsuccessful but we finally did experiments in the early 1970s in which we prevented colds by spraying our total supply of leucocyte interferon up the noses of 16 volunteers.[1] However, it needed the lapse of another ten years and the development of a galaxy of genetic engineering techniques before we could take this observation any further and prove that the effect was due to interferon itself and not a contaminant and then to start to work out the exact doses and means of administration which would make it possible to prevent naturally occurring colds.

SOME LESSONS

It is difficult to formulate what one has consciously or unconsciously learned by these various phases of professional life, but I

1. Merigan, T. C., Reed, S. E., Hall, T. S., and Tyrrell, D. A. J. 'Inhibition of respiratory virus infection by locally applied interferon', *Lancet*, 1 (1973) p. 563.

must try to do so as they affect in one way or another everything that follows. One lesson is that there is always something new and exciting to be discovered 'out there' and that the new almost always enlightens our understanding of the old.

The next two lessons have to be combined. The first is that it is extremely difficult and requires constant study, work, and attention to detail to become really good at any quite small area of endeavour, ranging from the clinical care of patients with infectious disease to the isolation of viruses from clinical specimens. The second is that we need to have a good idea of the principal lines of work in areas that impinge on our own and also the principles on which such work is done if we are really to understand our own results, and even more to foresee and make new advances. At the simplest level—advances in our field may well come if we apply techniques or principles which have recently been established in others. Often, however, we need high expertise from several fields and worthwhile advances can then only be made by collaborative research between a number of investigators supported with a full range of equipment—this is the basic reason for the existence of the modern multidisciplinary research institute.

As a way through some of these contradictions I have learned to value a firm grasp of principle even more highly than a good store of detailed knowledge. This may be illustrated by the occasions when a wise individual keeps on a study when it is initially disappointing because he perceives that it is directed towards an end which is in principle very important, and that the general line of approach is one which in principle will succeed. I could illustrate this by the way in which for fourteen years Sir Christopher Andrewes pressed to keep the Common Cold Unit going because he saw that combining studies on animals and tissue culture on the one hand and volunteer inoculation on the other, would eventually yield fundamental information about the cause of colds.

Although it is easy to get lost in a maze of detail it is important to remember that infection as we call it is but a special example of the way in which living creatures interact with each other, their ecology in fact. In our case this is usually how micro-organisms interact with man and other vertebrates. But each micro-organism is interacting with the whole vertebrate and often with other

micro-organisms and therefore virtually anything done by the vertebrate or the physician to improve things for the patient will be, for the micro-organism, a change in environment to which it will adapt—and the powers of adaptation possessed by most micro-organisms, even the simplest viruses, are indeed considerable.

I have also learned to be on my guard against superficial judgements about what is 'good' and 'bad' science. Many different activities result in the advance of natural knowledge and they are undertaken by many different sorts of people. The clinician asking himself why that person became ill, the epidemiologist working on national statistics, the genetic engineer making new molecules in a ferment of bright ideas and novel technology, and the field worker finding out how to get a vaccine to work in an African village, all are doing science and all are doing it well (or sometimes badly). If we have to rate science I think that in all fields the specially precious thing is a new idea or approach which will give purpose and value to the labours of a hundred individuals besides its originator, though here again a new idea or technique has not been proved of value until it has been taken up, evaluated, and applied in a variety of ways and circumstances, and each originator will affirm that what he or she has done depends totally on the painstaking and perhaps unoriginal work of many others. The annoying thing is that we seem to have learned how to train and (perish the thought) *produce* the hundred follow-up scientists but we must wait for the one originator to happen.

In spite of the emphasis on science and research I remain convinced that clinical observations and practice remain the most powerful intellectual and motivating reason for the study of the biomedical sciences. The areas of knowledge overlap in all directions and no one can comprehend let alone contribute to them all. A special contribution can be made by those who overlap areas. The day of the true generalist is gone for ever—all physicians are incomplete and so are all scientists, but it is agreed that there is great value in having individuals who are well trained in general medicine, but specialize in infection; the fact that they do not understand all aspects of all their patients does not endanger these patients since they know both when their knowledge and experience are inadequate to the task and whom they should call on to

give the best available care. We also need those who as far as their training, time, and intellectual capacity permit sit astride the areas of clinical practice and the underlying science and who can work effectively in both, using the same principle. We must not allow academic cuts and lengthy programmes for specialist accreditation to deprive us of that small number of clinician scientists we need and can support.

2

Infectious agents and their effects

THE DISCOVERY OF INFECTIOUS AGENTS

Down the ages physicians have been trained to recognize and treat infections. They observe sometimes the systemic effects, such as fevers and rigors, and at other times the local effects, particularly inflammation—as marked by *rubor*, *dolor* et *calor* (redness, pain and heat). It was slowly realized that certain of these diseases were communicable by human contact or by fomites; perhaps the classical example was the way the City Fathers of the Middle Ages recognized that plague followed the arrival of people or objects from affected areas and therefore developed the laws of quarantine—of forty days of isolation. According to Winslow physicians were more impressed with the importance of the individual constitution and locality in the aetiology of these diseases, while administrators were impressed with the way they spread by some form of contact. To break the chain of contact interrupted the spread of disease. The ideas were made much more precise and clear after the birth of bacteriology and then virology at the end of the nineteenth century. They revealed that self-replicating microscopic or submicroscopic organisms existed and could cause disease. The number and diversity of organisms found both in cases of disease and in the environment has continued to increase since then.

It is often implied that by now the causes of all bacterial diseases have been discovered but this is certainly untrue. In fact new pathogenic bacteria continue to be detected; for example, in the last few years research has revealed the Legionella as causes of pneumonia. These organisms were first cultured in eggs and thought to be Rickettsiae but they thrust themselves on our awareness after a dramatic outbreak of pneumonia in ex-servicemen attending an American Legion Convention.

The pneumonia was recognized as severe and all sorts of causes were considered, from viruses to toxic elements, but by first-class

bacteriology the organism was cultured and called Legionella. It is strange that an organism of this sort which is so difficult to grow in the laboratory should at times flourish in hot water supplies and central heating humidifiers but it seems that this is where it comes from, though strains have also been found in ponds and cases have followed immersion in swamp water. The severe cases usually occur in patients with underlying disease and outbreaks have occurred in several hospitals. If recognized in time erythromycin treatment leads to rapid improvement. Although the organism is certainly not 'new' it is likely that the changes in buildings and in medicine have encouraged the occurrence of cases so it is probable that Legionella pneumonia is both a new disease and a newly recognized disease.

Pathogenic viruses have been discovered too—in the last few decades literally hundreds of organisms, particularly of the intestinal and respiratory tract and new arthropod transmitted viruses have also been discovered. However, merely discovering a bacterium or virus does not prove that it causes disease; in fact, some viruses were called 'orphans' because they were at the time, soon after their discovery still 'in search of a disease'. By now many of these 'new' viruses have found their disease. For instance in the last decade a virus enterovirus 70 has emerged. In the laboratory it behaves like an echovirus, many of which seem to be harmless, but it was found in association with a disturbing new disease called acute haemorrhagic conjunctivitis which has swept around the world, particularly in the tropics, causing millions of cases. This appears to be a new virus and a new disease though it rarely causes serious illness or residue—occasionally neurological deficits have been seen.[1]

Other recently discovered viruses have been proved to cause significant and severe diseases. Names such as Lassa, Ebola, and Marburg disease are well known. They are all infections which come from Africa but have only been recognized recently. Lassa fever virus, for instance, is carried harmlessly by the multimammate rat, *Mastomys natalensis*, but caused a devastating epidemic of a viral haemorrhagic fever in a mission hospital in Lassa where

1. Higgins, P. 'Enteroviral conjunctivitis and its neurological complications', *Archives of Virology* (1982) in press.

there was a high mortality; other cases have occurred in the area and in individuals who have visited the area, travelled by air during the incubation period and fallen sick abroad, for example in London. The policy here, which is being reviewed at the moment, is to try to recognize cases early, handle the dangerous blood

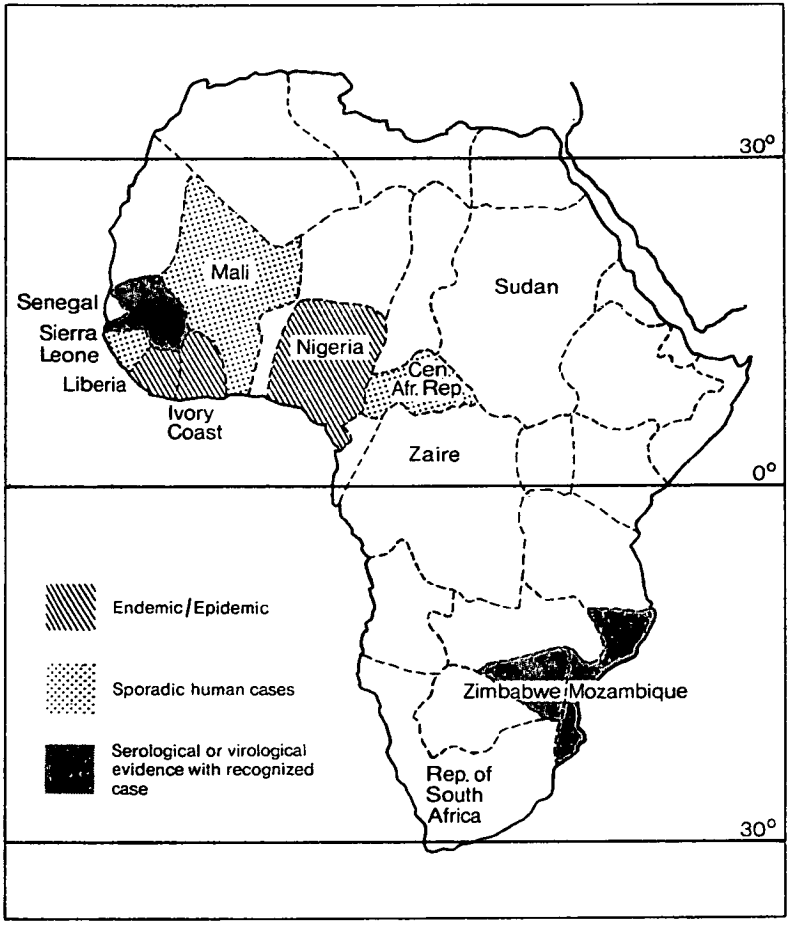

FIGURE 2.1. Distribution of Lassa fever virus and the related virus in Africa. Results of serological surveys and virus isolations. Kindly supplied by Professor D. Simpson, CAMR.

samples in a secure laboratory, and nurse the patient in a special high security isolator in a designated hospital. The virus is only isolated and cultivated in a top security laboratory at CAMR on Porton Down. This infection is probably not really new, previous cases in West Africa may well have been misdiagnosed as Yellow Fever, but it has become a typical example of viruses which emerge from tropical areas, and has required extraordinary care in the way it is handled.

There is naturally increasing concern about sexually transmitted diseases particularly conditions like 'non specific' in other words 'non-gonorrhoeal' urethritis which is common and can be difficult to treat. By definition no pathogens could be isolated in the past, but now up to half the cases have been shown to be associated with chlamydiae; ureaplasmas have been isolated, shown to be pathogenic, and responsible for a further fraction of the cases. Yet other causes are being discovered[1] and an unusual mycoplasma and a strange gram-negative bacterium, both of which are difficult to cultivate by the usual methods, are now under study.

Anaerobic bacteria such as Bacteroides have been reassessed in recent years, particularly as methods for culturing and identifying them have improved and it has been realized they are much more important than was previously recognized in causing sepsis in the lung and abdomen where mixed infections are common and the associated aerobes were previously blamed for the infection. As a result of this new understanding, treatment with more appropriate drugs, particularly metronidazole, has been used more often and patients have benefited.

This is a small and rather random selection but is intended to show that new organisms are being isolated and characterized regularly and many are being shown to cause disease. Judging by the number of unexplained infections and fevers one sees in clinical practice it is likely that more infectious agents remain to be found and if the search is able to continue, interesting and useful discoveries will continue to be made.

Many of the organisms mentioned are likely to be pathogenic

1. Tully, J. G., Taylor-Robinson, D., Cole, R. M., and Rose, D. L. 'A newly discovered mycoplasma in the human urogenital tract', *Lancet*, 1 (1981) p. 1288.

wherever they are found, but it is also clear that the environment, the health and nutrition of the host and so on alter the results considerably. It seems to me that the bacteria causing infections in developing countries may often be different from those we have here and I will return to this matter later.

THE PROCESSES OF INFECTION

It is often thought that the essence of research in infectious diseases is a search for the infectious agent which is 'the cause' of a condition. In the case I know best, common colds and related diseases, it turns out that these respiratory tract infections can be caused by any one of a hundred or so viruses, and even after they had been successfully cultivated and grown we have had to labour long and hard to assemble the facts to prove that they do cause such diseases and are not present by coincidence. Yet when one looks closely and critically at any one of these infections it is clear that there is a great deal that we still do not know about them. Working with human beings there are practical and ethical limits to what one can do to explore things further, but it is clear from volunteer experiments that many subjects are infected but do not get colds and this could be simply explained by seeing whether they carry antibodies, and therefore can be presumed to have acquired some degree of immunity from a previous infection. In some infections of this type, for instance, with influenza viruses, it is possible to do animal experiments, studying in detail the evolution of the infectious processes in mice, ferrets, or other animals. Older work showed how the signs of virus damage appeared in the mucosa of the airways and then lead on to pneumonia with lung collapse, infiltration with inflammatory cells, and death. Later on it was shown that virus was present in the damaged cells of the mucous membranes and subsequently in the alveoli. However, many new aspects of this process are still being revealed. For instance, by using recombinant influenza A viruses of different degrees of virulence, it has been shown that viruses multiply in the ferret's nose but are attacked by white cells and their growth is limited by the febrile response. It appears that the production of interferon may have an effect in some respiratory

virus systems but is not shown in this system. The immune response has also been studied in great detail. Antibody against the virus haemagglutinin (a major polypeptide) at the surface of the virus particle in the serum or in the secretions neutralizes the virus and protects the host against infection, while antineuraminidase antibody may not prevent infection but does reduce the spread of disease. Recently it has been shown that a special category of lymphocytes, the cytotoxic T cells, also play a part by destroying cells which carry influenza virus antigens on their surface, and if these lymphocytes are lacking the virus is not cleared from the lungs and indolent infection results. These lymphocytes become specifically sensitized by contact with viruses. Virus may also modify the function of neutrophils, this time to the disadvantage of the host, by impairing chemotaxis. This may be why a staphylococcal infection in the lung in association with influenza virus infection can be disastrous—large clumps of staphylococci may form and there are no signs of any polymorphs migrating in to engulf them. The lung contains pneumocytes which make surfactant—a phospholipid mixture which modifies the air fluid interface in the alveoli and prevents them collapsing. Virus damages these cells, less surfactant is formed and no doubt this contributes to the lung collapse.

This is a rather ridiculously brief survey of work on the pathogenesis of influenza but it serves to make the point that there is an area of knowledge, which includes some of the territory of microbiology and some of immunology and morbid anatomy but which, in order to be satisfying, must be multidisciplinary in the fullest sense and it is concerned with unravelling the full range of interactions between the host and the parasite and is often described as the study of pathogenesis. In recent years there has been quite a lot of research work that follows into this area. A sign of this is the appearance of new journals such as the well-supported *Infection and Immunity*, and the amount of material of this sort published in established organs such as the *Journal of Infectious Disease*. Indeed the Society of General Microbiology now has a Pathogenesis Group and The Royal Society is having a special discussion meeting on the subject in 1983.

In my view this is a very appropriate basic science to be studied

by a clinician who is dealing with infection, because the facts obtained often have important practical implications. One of these is in the development of new vaccines. Many of the older vaccines were made quite empirically but now that we can produce relatively pure antigens it is important to understand the role they play in the infectious process so we can decide which is the best to use. For instance in certain bacterial diseases of the intestine the organism sticks to the cells lining the gut and produces a toxin which damages the cells; thus it might be possible to protect by inducing antibody that is directed against the attachment site or the toxin, or perhaps both. Indeed, there is hope that this approach will succeed in giving us an improved whooping-cough vaccine. In the case of poliovirus infections it is well-known that the virus multiplies locally in the upper and lower alimentary tract before invading the nervous system via the blood stream. Thus low levels of circulating antibody may prevent paralytic disease, as was shown in the classic studies in the USA on the effect of human gamma globulin. On the other hand it was expected that parenteral vaccination with inactivated virus would not prevent the spread of infection, because it would not induce local secretory antibody. However, although live oral vaccine stimulates particularly strong local surface immunity it has been found that in countries such as Sweden in which only killed vaccine is used, wild viruses have ceased to circulate just as has happened in countries using live vaccines—there obviously is a significant amount of local immunity. Thus, although important principles can be learned from laboratory studies of pathogenesis and resistance, it is important to verify these in particular clinical situation and this is a strong reason for linking a study of pathogenesis with clinical research.

The study of pathogenesis also enables one to consider in some detail the way in which the reactions of particular cells and tissues determine such things as the usual route of infection and the infectious dose, and the type of disease produced. For instance, we studied the growth of a variety of viruses in organ cultures, that is, surviving pieces of human tissues. It turned out that the 'respiratory' viruses would grow freely in cultured epithelium of the nose or trachea, but not in cultured skin, whereas viruses like

herpes simplex and vaccinic viruses would grow in skin. Thus it is clear why cold viruses are not prone to spread and cause ulcerating lesions of the face—we say 'of course not', but that only means that we have become used to the observation, not that we understand what it implies. Other experiments show that the growth of rhinoviruses is usually strongly inhibited by temperatures much above the usual temperature of the nose, i.e. 33° and this probably explains why they are found causing colds, that is, infections of the upper respiratory tract and not lower respiratory tract disease, in which they would need to replicate in an environment near to the core temperature of the body. For some aspects of the pathogenesis of influenza viruses we are already beginning to express things in molecular terms. Elegant studies by Rott and his colleagues have shown that influenza viruses are only fully infectious when the haemagglutinin peptide has been cleaved by a proteolytic enzyme and they have shown in an experimental system that those strains that are virulent are those of which the haemagglutinin is cleaved by the enzymes of the host cell and that in those that affect different tissues the infected tissues are those that cleave the haemagglutinin.

It is also fascinating to consider the maintenance of the normal flora of the body. In some places, such as the blood, urinary tract, and the sub-arachnoid space, microbes are almost never found in health—the mucous membranes and their supporting phagocytes and humoral factors are an effective barrier. Yet on the surface of the skin and mucosae a wealth of bacteria and some viruses can be found living on scales, secretions, and bowel contents, and apparently causing no harm. Indeed they may be helpful in that it is common experience that when they are removed, for instance by using broad spectrum antibiotics, a variety of other organisms, bacteria, or fungi, may replace them and cause disease when in the presence of the normal flora they can do neither.

It is clear that the body secretions provide a culture medium which determines to some extent which organisms can survive and which will predominate. The fatty acids and the dry conditions probably control the flora of the skin, and the vaginal flora changes as the secretions change in response to the hormonal fluctuations during the menstrual cycle. It is now clear that the harm-

less flora of the mouth is changed by a diet rich in sugar to one which generates dental caries, so that the disease can be controlled either by vaccinating against the bacterium or by preserving the normal flora by providing a well-balanced diet.

Finally, some studies of pathogenesis may illuminate unexpected epidemiological observations. Dengue virus infections are ordinarily manifested as unpleasant but not dangerous febrile illnesses. However, there has been in the Pacific Region a worrying increase in a severe form with haemorrhage and shock. This is not fully understood but it is apparently associated with infection of an individual by a second serotype of virus (out of the four circulating) which has become a more common event as dengue viruses seem to be increasing their range. Scott Halsted has what seems to me to be the most likely explanation for this, namely that low concentrations of antiviral antibody *increase* the extent of infection with these viruses. They replicate in macrophage type cells and it is probable that virus combined with antibody is more readily attached to its host cell because this antibody links to the FC receptor that it bears. So children carrying small amounts of cross-reacting antibody from a previous infection with a related serotype are particularly liable to have fulminating and dangerous infection.

3

The importance of the host

It is also important to consider the overall state of the patient and his defensive mechanisms. This is the modern version of the old physician's concern with the patient's diet, way of life, and where he lived. We have already mentioned the remarkable way in which the various areas of the body are kept either free of microbes or covered by a relatively stable and harmless 'normal flora'. In modern practice patients with damaged organs are treated by new and powerful immunological methods to prevent them rejecting tissues transplanted from another individual and thus it is possible to successfully graft a new kidney or bone marrow. This may succeed but thereafter the patient may die of a severe virus or other infection; indeed immunosuppressed patients of all sorts commonly form an important segment of hospital patients suffering from serious infections—and it is clear that this is due to the impairment of their immune mechanisms. The reason is not far to seek for the 'cell mediated immunity' that has to be suppressed to prevent rejection of engrafted cells is essential for containing infection with organisms such as the herpes viruses and fungi. It seems to me that one way out of this problem is to refine the methods of immunosuppression. For instance it has been shown in Oxford that reducing the amount of steroid given reduces the frequency of virus infections without an increase in the number of rejection episodes. It would also be desirable to find methods that ablated the response to the graft without affecting the ability of T cells to respond to other antigens. Some promising studies have been done in animals but I know of no evidence that it can be done in man yet. Meantime, we need to use all our skill with antibiotics, sterilization of food, and care with barrier nursing to keep the number of these infections down as far as possible. Even without the effect of drugs or serious disease the resistance of the individual changes during life. Immune mechanisms are immature in the first months of life and decline, like other body functions,

at its end and this is why severe infections are seen in infancy and old age and are uncommon in between.

Sometimes it may seem to be possible to ignore the state of resistance of the host. For instance, in the past it was essential to encourage general health and resistance in order to treat patients with tuberculosis successfully, but now that very potent antibiotics against *M. tuberculosis* are available it is possible to obtain good results in many cases simply by giving a good drug regime and not changing the patient's lifestyle or environment. However, this is not to deny that before the days of antibiotics, patients

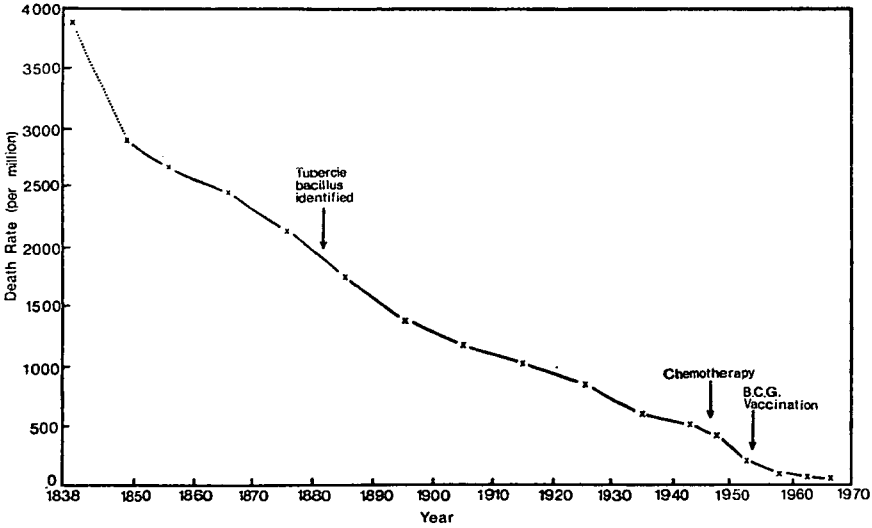

FIGURE 3.1. Respiratory tuberculosis in England and Wales—mean annual death-rates standardized to 1901. Reprinted by permission from McKeown, T. *The role of medicine: Dream, mirage or nemesis?* (The Nuffield Provincial Hospitals Trust, 1976).

were helped to conquer their infections by a regime of rest, good food, and fresh air. Indeed, if we look more carefully at the community as a whole it may be that these general factors have done more than we give them credit for and bacterial diseases have not been defeated solely by the use of antibacterial drugs. It has been pointed out repeatedly that the decline of infectious diseases in

Britain since the mid-nineteenth century may have had little to do with specifically anti-infectious measures. The sanitary movement which began in the early nineteenth century was motivated by a wish to get rid of filth and odours and improve the environment generally, but the results of their efforts interrupted faecal-oral transmission by providing drains and piped water and reduced the frequency of intestinal infections. But it is likely that other less well defined changes, probably in housing and diet reduced the mortality of diseases such as whooping-cough, measles, and tuberculosis; certainly they were declining before measures such as vaccination or antibiotic treatment had any effect. One theory that appeals to me, though I have never heard it discussed, is that the ideas on nursing promoted by Florence Nightingale were beginning to be applied in the home. If sick children were rested, given more fluids and nourishment, and temperature controlled then perhaps that would improve their chances. A recent analysis has shown that the occurrence of rheumatic fever and rheumatic heart disease, which follow infections with certain streptococci, have remained frequent in the developing countries of the world where conditions are probably quite like those of eighteenth-century Britain but where rapid economic development has occurred, as, for instance, in Hong Kong, Singapore, and Japan there has been a simultaneous and rapid decline of these two diseases. In this case, of course, medical care must have improved too but I doubt if that alone can explain the changes. A converse phenomenon has been seen, namely that after personal stress individuals are prone to infection—there is a real truth in the way that in the cliche, 'war and famine' are followed by 'pestilence'. Refugees from Uganda had been mostly well fed and housed and then came to Britain in the early 1970s. They showed a greatly increased incidence of tuberculosis, though the strains they were infected with were acquired in Britain. It was found that some of them with florid disease failed to show signs of an immune response by either skin test or lymphocyte response and this is presumably why the disease was progressing. Sometimes after treatment for a while the immune response seemed to develop quite suddenly and they felt worse, because of the inflammation in infected tissue and the fever. However, we used to regard that as

a good sign indicating that a satisfactory host response had returned. It has also been shown that an accident and admission to hospital can change the types of bacteria found in the pharynx, though how this is mediated is unclear. Though the overall phenomena are well recognized the detailed mechanisms are still, in my view, quite obscure, and are mostly subjects for future research. Students are often taught as though the effect of stress on the secretion of hormones and their adverse effect on resistance to infection were an adequate explanation for the phenomena. We have recently found that quite mild stress produced either in normal life or in experiments can enhance the severity of colds in volunteers.[1] As part of these studies it was also found that introverted volunteers shed more virus than those with extroverted personalities and I have no idea of the connections between the two. It is well recognized that minor respiratory infections, coughs, and colds are very frequent, and influenza epidemics are a recurrent bane—the latter is the only disease that can, in developed countries, produced a marked change of daily activities in communities and a significant peak in the national mortality statistics. Bacterial diarrhoea and related diseases have greatly declined, in all probability because of the improvement in the quality of water supplies and of food hygiene, although severe diarrhoea still occurs in children due to the activity of the rotaviruses, which it seems may spread by the respiratory route. This fits with our general idea that nutrition and environment do not affect the frequency of respiratory infections so much. If normal family and community life continue the airborne spread of organisms will continue too. The persistent sociability of man will ensure that these organisms, mostly viruses, will not decline in incidence as enteric infections have done.

On the other hand, a whole group of infections, which in the past have been studied quite separately, are increasing steadily in frequency and changing steadily in clinical presentation and this seems to be related quite clearly to changes in behaviour of the host. I refer to sexually transmitted diseases[2]—and although

1. Totman, R., Kiff, J., Reed, S. E., and Craig, J. W. 'Predicting experimental colds in volunteers from different measures of recent life stress', *Journal of Psychosomatic Research*, 24 (1980) p. 155.

2. Caterall, R. D. 'Biological effects of sexual freedom', *World Health Forum*, 2 (1981) p. 528.

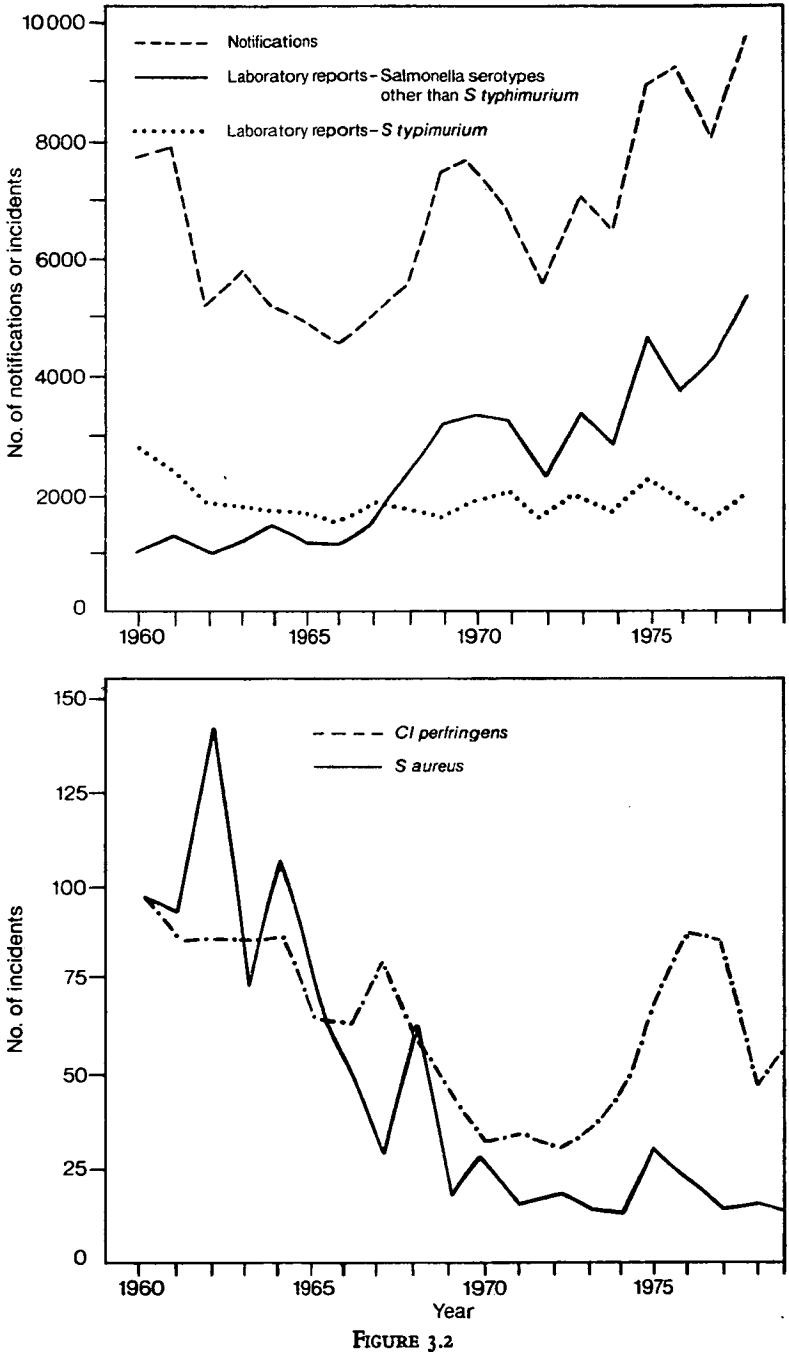
10 000
8000
6000
4000
2000
0
No. of notifications or incidents
Notifications
Laboratory reports – Salmonella serotypes other than S typhimurium
Laboratory reports – S typimurium
1960
1965
1970
1975
150
125
100
75
50
25
0
No. of incidents
Cl perfringens
S aureus
1960
1965
1970
1975
Year

FIGURE 3.2

syphilis is still rare, gonorrhoea and genital herpes are common and non-gonorrhoeal urethritis is now the most commonly notified infection in England. It is a subject about which thinking and the expression of thought are much constrained by emotion and social pressures. It is common to laugh at the prudery of the Victorians (which must certainly have contributed to their inhibitions and neuroses in sexual matters), but also at the more ancient views of monogamy and premarital chastity which most of them supported, in theory at any rate, and which they ignored at the cost of disastrous disease such as general paralysis of the insane—when that disease was recognized forty per cent of the patients in a mental asylum in Paris were suffering from the disease, i.e. tertiary syphilis. I have come across a different sort of taboo at the WHO where we were not allowed to introduce the word 'promiscuity' or mores into a report but had to use circumlocutions such as 'behaviour patterns'. Such issues apart, in the name of freedom, mental health, greater experience, and fulfilment, a substantial proportion of young people have frequent coitus often with a number of partners and by a number of routes. It is also common to rely on oral contraceptives to prevent pregnancy rather than barrier methods. Thus the transfer of pathogenic organisms occurs much more frequently than before. Although medical treatment is freely available there is an impression that follow-up of the consort is often less effective than it used to be. I think it is unlikely that these diseases will be reduced in incidence unless there are changes in behaviour which will probably only follow changes in attitudes. From the medical point of view it is unfortunate that those who had advocated these changes did not foresee, or did not choose to mention, these infectious consequences, which include not only acute infections, but later sequelae including chronic prostatitis and pelvic infections, involuntary sterility, and arthritis.

FIGURE 3.2. Food-poisoning in England and Wales. Upper panel shows notifications and reports of salmonella infections and lower panel laboratory reports of *Staph aureus* and *Cl perfringens* infections. From Galbraith, N. S., Forbes, P., and Mayon-White, R. T. 'Changing patterns of communicable disease in England and Wales. Part III—Increasing infectious diseases', *British Medical Journal*, 3 (1980) p. 546.

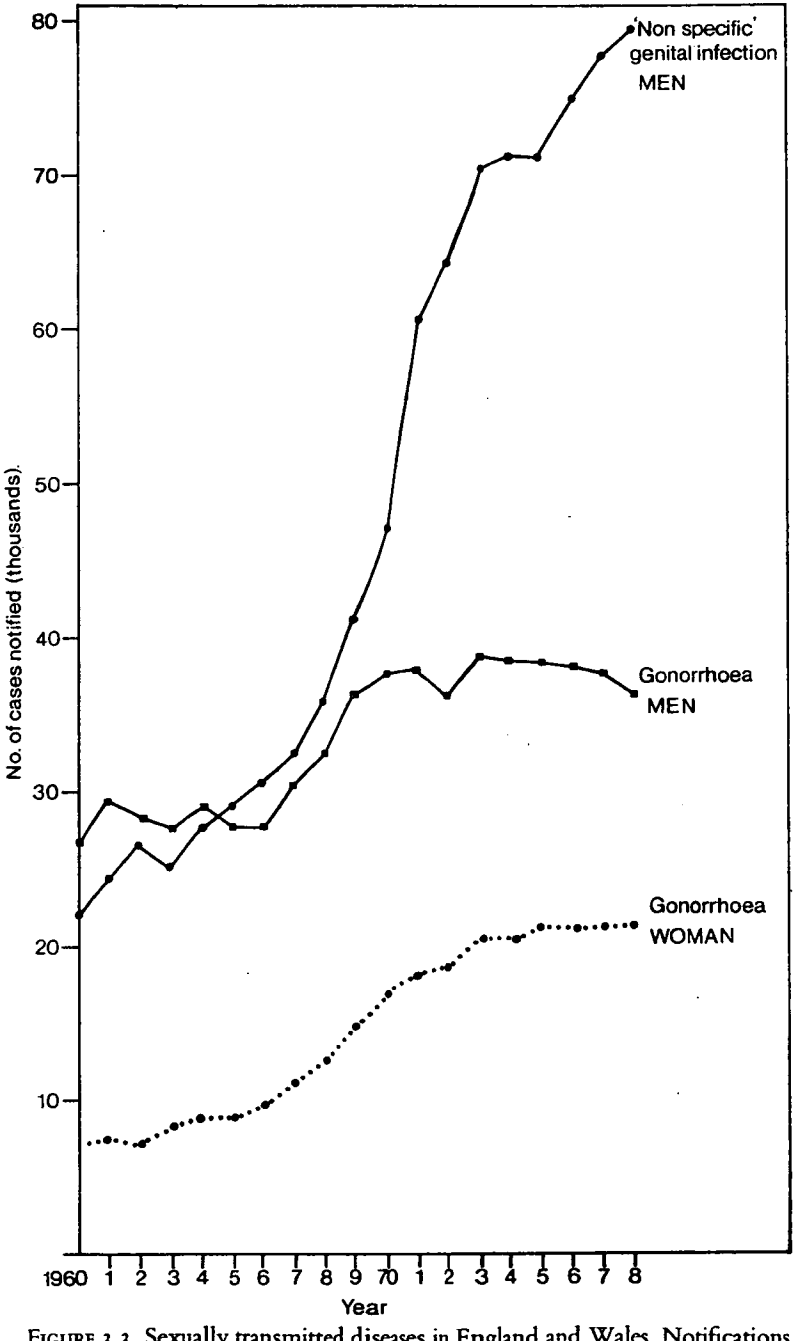

FIGURE 3.3. Sexually transmitted diseases in England and Wales. Notifications. Drawn from data of Galbraith, *et al.*, (1980).

Other changes have followed the legislation which eliminated the official restraints on homosexual practices and the social pressure in some quarters for individuals with homosexual tendencies to express them. It seems virtually certain that there has been a substantial increase in homosexual practices, among males at least, some of whom are particularly promiscuous. It has been demonstrated that in these circumstances hepatitis B is frequently transmitted. It has just been recognized that in addition to this such patients may acquire immunodeficiency, possibly because of aerosol drugs taken to enhance sexual potency and as a result a characteristic major illness including infections with cytomegaloviruses and a particular form of Kaposis sarcoma may appear.[1]

Thus it is essential when considering the causation and diagnosis of infectious diseases to remember the crucial role of the host, and even when preventing or treating disease it may be that to support the host is more important than to attack the microbe directly.

1. Hymes, K. B., Cheung, T., Greene, J. B., Prose, N. S., Marcus, A., Ballard, H. B., William, D. C., and Laubstein, L. J. 'Kaposi's sarcoma in homosexual men—a report of eight cases', *Lancet*, 2 (1981) p. 598.

4

Antibiotics and other drugs

While those interested in infections may see the situation as developing and changing as I have just described, old diseases going and new problems and treatments coming in, many others see things quite differently. A prime factor in the mind of both the public and the professions is the introduction and the powerful effects of the antibiotics. These have dramatically altered our view of many diseases—streptococcal septicaemia can be completely cured in a matter of days with penicillin; subacute bacterial endocarditis is no longer uniformly fatal because a variety of antibiotics can be deployed to treat it; on diagnosing tuberculosis one tells a patient that provided he takes his tablets of antibiotics and other drugs and co-operates for a year he will assuredly recover. This has lead to a common view that bacterial infections are no longer a clinical problem. On the other hand, virus infections are in general untreatable, but the serious diseases such as poliomyelitis, smallpox, and yellow fever can be effectively and simply dealt with by vaccination. This view of the situation is, of course, confirmed by seeing infectious disease and tuberculosis hospitals which have been closed or used for treating uninfected geriatric or other patients.

There are, however, other ways of looking at our attack on the infections and these are not so comforting.[1] For instance, it is well recognized that when populations of pathogenic bacteria are exposed to antibiotics they respond like other organisms to combat this adverse factor in their environment—expose a population of penicillin-sensitive staphylococci to penicillin in the laboratory and penicillinase-producing staphylococci become common and animals experimentally infected with such organisms do not respond when treated with penicillin.

Similar phenomena have been observed in the general population of this country not once but many times. New penicillins

1. Levy, S. B. 'Microbial resistance to antibiotics', *Lancet*, 2 (1982) p. 83.

such as ampicillin were introduced and given for many purposes and after a decade a high proportion of organisms such as *Haemophilus influenzae*, which can be serious pathogens especially in children, are now ampicillin resistant, so the drug is no longer suitable for treating such infections in the majority of cases. This has not happened only in the UK. Sulphonamides were the ideal

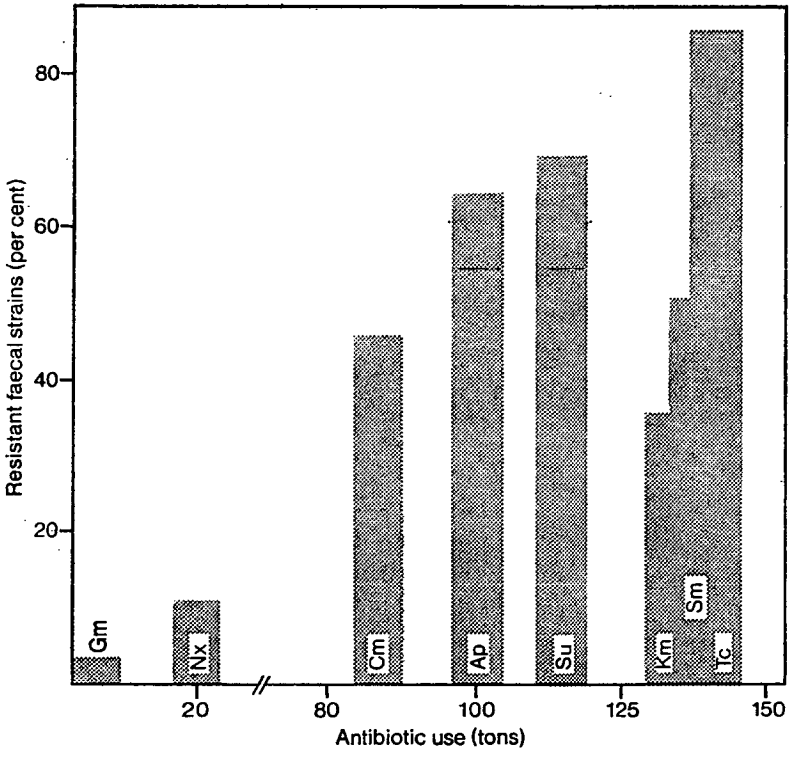

FIGURE 4.1. Antibiotic consumption and bacterial resistance. Correlation between antibiotic use in a country and resistance carried by 295 *E. coli*, 198 *Proteus mirabilis*, 63 indole-positive *Proteus* spp, and 30 *Salmonella* strains isolated from diarrhoea specimens in Toluca, Mexico, in 1977. Gm = gentamicin, Nx = nalidixic acid, Cm = chloramphenicol, Ap = ampicillin, Su = sulphonamides, Km = kanamycin, SM = streptomycin, Tc = tetracycline. From Figure 3 of Levy, S. B., 'Microbial resistance to antibiotics. An evolving and persistent problem', *Lancet*, 2 (1982) p. 84.

drug for treating that scourge of Africa south of the Sahara, meningococcal meningitis; now a high proportion of organisms there are sulphonamide resistant and even in the UK there are enough such strains for most physicians at least to start treatment with penicillin.

But it is probable that such changes are not inevitable—at least not always and on a large scale. Various strategies have been proved to work. One is to use combined therapy as is done in tuberculosis—if a microbe mutates and becomes resistant to one drug it will be unable to multiply freely and spread to others because of the presence of another drug. Another strategy focuses on interrupting transmission of resistant organisms; in our hospital when a patient is found to have an infection with any organism with multiple antibiotic resistance he or she is strictly isolated to prevent it spreading to others and so far the measure has succeeded. A further method is to have a well-thought-out and well-applied antibiotic policy for a hospital. The frequency of erythromycin-resistant organisms was increasing rapidly after the drug was introduced but certain hospitals decided to use it only in cases where it was badly needed and not to use it when there were good alternatives. As a result the frequency of resistant organisms fell again and the drug could still be useful.

The problems persist where control is impossible or ineffective. The increase of ampicillin resistant *H. influenzae* in the population was probably a result in part, of giving the drug for urinary tract infections—for entirely appropriate reasons. However, the number of individuals who had antibiotic resistant *H. influenzae* in the throat would be likely to increase from then on and could pass the newly selected organisms on to others. No doubt this also happened when such drugs were given inappropriately, for instance, for virus infections of the respiratory tract. One cannot blame only the prescriber. A most effective way of selecting antibiotic-resistant organisms is to give low doses for a short period, so patients who take less than is prescribed and do not complete the course (and it is known that non-compliance of this sort is common) may contribute to the problem.

When I started in practice it was noteable that pneumococci and gonococci were always sensitive to penicillin. But in recent

years very penicillin-resistant gonococci have emerged, particularly in developing countries, and organisms with the same β lactamase enzyme are being found around the world; furthermore, highly resistant pneumococci have been detected in Papua New Guinea and in South Africa may do the same. Furthermore, these are not academic matters; patients infected with these organisms fall sick and do not respond to treatment with penicillin which is ordinarily dramatically effective.

However, there are more serious matters to report. Much publicity was given to the way in which the use of antibiotics in feedstuffs to improve the live-weight gain in calves and poultry selected antibiotic resistant organisms such as Salmonellas in livestock and that these then infected man. Indeed, the Swan Committee considered the matter and reported on it in detail. Antibiotics were removed from feedstuffs but the problem has not gone away, possibly because the drugs are still used for treatment or possibly because, unlike other situations with some other antibiotic-resistant organisms, in this case resistant organisms are not at a disadvantage in other respects and so they continue to survive even when the selective factor which brought them to prominence has been removed.

Studies in Japan some years ago revealed that antibiotic resistance in enteric bacteria could be transmitted from one organism to another by plasmids or R factors which may be thought of as small pieces of DNA which can be transferred from bacteria to bacteria rather like viruses and which can carry genetic information of many sorts with them into their host cells. Thus they perform for bacteria some of the functions of sexual conjugation in higher organisms. Antibiotic resistance may also be encoded in the chromosomes or in small pieces of DNA called transferons that can 'hop' from chromosome to plasmid and back again.

Plasmids can transfer antibiotic resistance in the bowel as well as in the laboratory and from one species of bacteria to another. Some plasmids encode the information for resistance to a wide range of antibiotics and apparently do not disadvantage the organism in other ways. The spread of these R factors seems to be the biological basis for the extensive spread of multiple resistance to antibiotics, for instance, in the tropics, the Pacific, and India. The

resistance of pathogenic enteric bacteria to antibiotic can have serious clinical effects. A dramatic early example was the appearance of chloramphenicol-resistant typhoid bacilli in Central America. Chloramphenicol is ordinarily a very satisfactory drug for treating such patients, but in these circumstances it had no effect and mortality was high. Thus an 'epidemic' of plasmids among the bacteria could lead to epidemics of disease in man which do not respond to the usual drugs.

What should we think? What should we do? I am sure we should eschew extreme views. On the one hand we should not say 'I told you antibiotics were no good', ignoring the great good they still do and suggesting that they should be abandoned; nor on the other hand should we say that no real problem exists and that in due course if we carry on as we are doing all the difficulties will go away. However, we are likely to succeed in containing the problem only if we use all the tactics open to us—there is no one simple and easy way out. We need to tighten up on our use of drugs in domestic practice as indicated above—and patients should learn not to press for antibiotics for minor ills. We need to monitor the appearance of highly resistant organisms in hospitals imported from abroad and to take stringent action to prevent them spreading and getting established if they are detected. Wherever possible we should deal with problems without employing antibiotics. I shall mention later the treatment of patients but it is clear that in this country antibiotic resistant typhoid is never likely to be a problem since we control the disease fundamentally by preventing transmission using food and water hygiene and the isolation of cases. This plus vaccination might well be a good strategy to press in areas where the organisms have arrived and cannot be handled with new antibiotics.

Finally, we need to encourage research for the development of basically new antibiotics. We need a few of these rather than a number of slightly better penicillins, aminoglycosides, etc. On the other hand as virtually all such advances are made in pharmaceutical laboratories and paid for out of profits we need to find a way of operating our health services without pushing the price of drugs down too far; the costs of introducing a new product and getting it through the regulatory agencies are so high that it

could become commercial suicide to try to fund a long-term basic search for new products. Nevertheless in the long-run it seems likely that our drugs will become gradually less useful and we need to develop new ones if we are to retain our capacity to treat infections.

In one area valuable new drugs are on the horizon which should enable us to treat infections with which we have had little or no success in the past. I refer to antivirals. In the last twenty years work which has gone on quietly has shown that virus infections are not as untreatable as was once thought. Influenza can be treated by oral administration of the drug amantadine and some local herpes virus infections can be treated with drugs such as idoxuridine. For the latter we have a new generation of therapeutic substances. Acyclovir is able to inhibit the growth of several herpes viruses at low concentration and it is very non-toxic because it only becomes converted to an active form when it enters a virus infected cell. It has been licenced for intravenous and local treatment and has already proved its value in herpes virus infections in immunocompromised hosts, such as patients being treated for cancer. Other substances with related modes of action are in various stages of development. Steady small-scale work on human interferon, mostly made from white cells obtained from blood donations, has shown that it can be used as an antiviral in similar herpes virus infections and also to prevent rhinovirus colds in volunteers.[1] Suddenly large amounts are available for research because interferon can now be made by 'genetic engineering' techniques, and if proved useful they could be manufactured in this way for widespread clinical use. Much careful development work is needed before this can happen. We need to work out how to administer interferons, how often, and in what doses. We should find out the advantages and disadvantages of the different sorts, not only their effectiveness in treating different virus infections at different sites but also the extent to which they produce unwanted general or local 'side effects'. We can assume that if antivirals are used antiviral resistant organisms will be encouraged. We know that organisms resistant to some antivirals can be found

1. Scott, G. M., and Tyrrell, D. A. J. 'Interferon: therapeutic fact or fiction for the 80s?', *British Medical Journal*, 280 (1980) p. 1558.

in the laboratory and in patients and the mechanism of their resistance has already been studied in some instances. Let us hope we are careful enough in our use of these new resources to develop their usefulness to a high degree and to so employ them that this is retained for a long time to come.

5

Infections that are often overlooked

INFECTIONS IN THE WIDER WORLD

It is easy to be much impressed by the decline of infections in Britain, Europe, and other developed countries and not to be aware of the fact that in the world as a whole there has been really little or no improvement; in fact, the number of infections is probably increasing as the world population climbs.

Statistics are understandably incomplete but in most developing countries acute diarrhoeal diseases go largely unchecked. The impact is particularly high on children and it has been estimated that there are twenty million deaths per year. Acute respiratory infections also kill and it is estimated that several million children a year die from diseases classified as pneumonia, bronchitis, and so on. Both these represent groups of infections, probably with viruses or bacteria or both. However, certain single infections also cause a heavy load of chronic disease, such as tuberculosis and leprosy, malaria and schistosomiasis—although the latter two organisms are protozoa they are nevertheless regarded as infections. Indeed it is significant that many of the special programmes of the World Health Organization, and in particular those on tropical diseases, are concerned with infections.

It is interesting and important that these diseases are not being attacked by a single method. Diphtheria, whooping-cough, and measles can be controlled by vaccination in childhood, so the extended programme of immunization, the EPI, focusses on providing potent cheap vaccines which are stable at refrigerator temperatures and then on ensuring that the 'cold chain' by which vaccines are transported reaches out to remote villages, and that a proper organization is built up for giving the vaccines and checking the whole system; there can be no benefit unless both the vaccines and the organization for administering them are effective.

In other infections transmission may be prevented, and this is the rationale for providing protected wells to prevent waterborne diseases, and is also the probable reason that the eye infection trachoma is lessened in houses with access to an adequate supply of clean water and where as a result the inhabitants are able to practice better personal hygiene. Of course, specific treatment can also make a dramatic contribution. Leprosy can now be treated effectively with oral drugs and patients can continue to live their normal lives, while louse-borne epidemic typhus can be cured with a single dose of antibiotic. However, one of the most effective treatments for a group of infections largely ignores the infecting organism. I refer to the use of oral rehydration in diarrhoeal diseases. This started with decades of research on the abnormal physiology of cholera, which showed that death was basically due to the loss of fluid and salts through the bowel, and that if these were replaced by intravenous infusion then virtually all patients survived. It was then found that the absorbative mechanism of the bowel was intact and that a mixture of glucose and electrolytes given by mouth would also save patients provided they were not too ill at the time administration began. Finally, it was found that the treatment was effective in almost any diarrhoeal disease, and so throughout the world now there are centres where the simple method of management and supplies of the solution are being provided. Further work is being done on the solution and a recent study showed that a mixture of rice-flour and salts was as good as the other solutions, and obviously easier to supply in certain areas. This illustrates an important fact, that sometimes a long and apparently esoteric investigation can lead to such a profound understanding of a disease problem that a simple and effective method of treatment can be developed and applied.

Sometimes what needs to be learned is even less tangible; although the WHO programme for smallpox eradication was in the end a resounding success, it is not always realized that its early phases partially failed in that the disease persisted in spite of mass programmes by which most of the inhabitants of a country were vaccinated. Then it was found that the virus was passing from person to person in under-vaccinated pockets of the country where their lifestyle and behaviour was different from that of the

bulk of the population—for instance nomadic tribespeople. What was needed was to concentrate on the areas in which cases were occurring and to bend every effort to find each case and to vaccinate everyone in contact. Two technical advances also contributed; one was the supply of freeze dried vaccine which retained its potency under poor conditions and the other was the discovery of the bifurcated needle with which almost anyone could learn to perform vaccination after five minutes instruction. When these innovations were made the chain of transmission was broken in one country after another, and finally in 1977, in the world as a whole, smallpox was eradicated.

This also illustrates another valuable principle. In countries like Britain it is possible with imperfect knowledge to deal with the multi-facetted problems of infection because we can find resources to treat the case or tackle the community problem in several ways. In my view the situation in developing countries is much more demanding scientifically since their resources are so limited that it is possible to implement only one measure—it is, therefore, crucial that these little resources are not wasted and that the decision on what action to take is based on well-founded evidence that it will be effective, and furthermore the best action for the particular people and situation. It seems that the management and treatment of acute respiratory infections is an example of this. For instance, it is widely believed that acute otitis media requires active treatment—in Britain usually antibiotic treatment and in other places myringotomy. However, this is a matter which has not really been fully investigated scientifically. Only recently a carefully designed controlled study done in Holland was reported and this showed that neither treatment alone or in combination had a significant effect on the course of the disease. This is probably a good basis for deciding that children with this disease should be treated with simple measures such as aspirins and hot drinks. It might also be a reason for saving money on antibiotics for patients in developing countries; but it is at least possible that only the worst cases come for treatment there, or that the children in developing countries are less able to control bacterial infections than those in Europe, thus antibiotics might really be beneficial and therefore a similar investigation is badly

needed in developing countries. One of my favourite illustrations of this sort, that I have inflicted on a number of ward-rounds is that of the vanishing herpes virus infection of Capetown as related to me by Professor Arthur Kipps. In the early 1960s it was recognized that seriously ill children were being admitted to the children's hospital suffering from a generalized infection due to herpes simplex virus involving the liver and that this was often fatal. It was realized that all the children came from the Cape Flats area and as the infection was untreatable plans were laid to make a herpes virus vaccine and to prevent the disease by vaccinating the group at risk. However, quite suddenly the disease disappeared, and on investigation it was found that the apparent reason was that a voluntary group, with no thought of preventing infection in mind, had arranged and begun to operate a method of supplying milk supplements to children in the area. An improved supply of proteins and calories probably had a better effect on the virus infection than a vaccine would have had, or even than modern chemotherapy could have achieved. This is relevant both to the matter of choosing the one best method of tackling a problem and also to the previous section on the importance of the host.

'SLOW' VIRUS INFECTIONS AND CHRONIC DISEASES

It has been known for many years that after virus infections such as poliomyelitis or encephalitis patients may suffer from long-lasting neurological symptoms and deficits. The classical example is perhaps poliovirus, and in such cases it was established that the neurological phenomenon was a result of the total and irreplaceable loss of motor neurones infected by the virus. However, even before modern virology was applied to the problem there were questions in the minds of some people as to whether this was a complete account of what happened. I recall talking to an anatomist who asked why there should be foci of lymphocytes and perivascular infiltration in the CNS many years after an attack of poliomyelitis; I also read the classical paper on mouse poliomyelitis by Max Theiler, who clearly showed that he could detect live virus in the spinal cord months after an acute infection and

clinical recovery. So it was possible that host response and virus infection might continue well after the acute phase was over. However, there was good clinical evidence that if neuromuscular function had not recovered within about a year after onset it was unlikely to do so later.

It was, therefore, an important conceptual advance when the Icelandic veterinarian Sigurdsson described his concept that there are 'slow virus' infections which cause progressive diseases of the CNS of farm animals. It is now well-known that one of these diseases, scrapie, is due to a very strange virus-like organism, that after a long incubation period causes a spongiform encephalopathy in susceptible animals. The work of Gajdusek and associates showed that a very similar transmissible agent or agents causes the chronic degenerative disease of kuru in Papua New Guinea, and Creutzfeldt Jacob disease in most other parts of the world. But chronic diseases are not only the result of infection with specially slow growing viruses. It is also clear that quite 'ordinary' viruses can cause serious CNS disease; for example, measles virus can grow progressively in the nervous system and cause the deadly and distressing subacute sclerosing panencephalitis (SSPE). This affects children years after they are attacked by measles and, incidentally, seems to be declining where measles vaccination is effectively practised. Thus we have ceased to think of virus infections only in relation to acute disease but also as causing important slowly progressive disease, even some which in the past were called 'idiopathic' or 'degenerative'.

It is probable that in some CNS disease the pathogenesis is complicated. The work of Ter Meulen and his colleagues suggests that in their model of demyelinating disease in the rate the lesions are due to autoimmunization of the animal against CNS antigens; this is provoked in certain genetic types of animal after the CNS has been infected at a particular age with a particular coronavirus.

Thus the importance of the phrase 'slow virus infections' is that there are combinations of virus and host in which infection recurs or progresses slowly rather than that there are any truly 'slow' viruses—though scrapie and related organisms might be regarded as an exception.

We have learned a great deal about the mechanisms by which

viruses can persist in the host and these are clearly varied.[1] Virus may persist in the circulation and produce no harmful effects (e.g. lactic dehydrogenase virus in mice) or the nucleic acid of DNA viruses may be incorporated into or attached to the nucleic acid of the host cell—(e.g. Epstein-Barr virus). Certain RNA viruses (retroviruses) produce a DNA copy which can be so incorporated. However, there are many examples which we do not fully understand and in some instances it seems that the virus simply replicates at a relatively slow rate in such a way that it produces little or no damage. It has been found by using 'rescue' techniques that herpes simplex viruses, or parts of their genome, can be detected in the autonomic ganglion of apparently normal subjects, and there is evidence for the presence of nucleic acid of herpes virus in the CNS of patients dying with nervous system disease. These findings need a great deal of confirmation and evaluation, but it may well be that these resident viruses may be involved in chronic and so-called idiopathic diseases.

It is fascinating to consider the various ways in which such a situation might develop. Oldstone and his colleagues have shown how an antibody response might enhance the persistence of the virus in the cell while inhibiting the production of infectious particles and have indications that while such a chronically infected cell may perform all the usual functions of a cell such as oxidative metabolism and overall protein synthesis they may be unable to perform what they call 'luxury' functions, such as producing enzymes concerned with neurotransmission, which nevertheless may be quite essential for the specialized function of a cell and for the survival of the host.

There are other forms of slow chronic encephalitis due to identified viruses, but I do not see why the list should stop there. It was suggested a long time ago that as a schizophrenia-like condition might occur in known cases of virus encephalitis the common type of schizophrenia might also be due to a virus infection. However, after many years of search to look for virus particles or antibodies against them, the use of a wide range of standard techniques has not revealed the presence of a virus, and perhaps it was

1. Mahy, B. W. J., Minson, A. C., and Darby, G. K. (eds). *Virus Persistence* (Cambridge: Cambridge University Press 1982).

rather naive to think that it might. What we can expect to find is either a limited and possibly localized infection with a common virus, in which most of the manifestations of a virus infection are missing, or invasion with an unusual agent analogous to scrapie but not necessarily the same. There are indications that the first may be true of some patients who seem to have an excess of cytomegalovirus antibody in the CSF, possibly IgM, and this would suggest that the virus is in some way resident in the brain. We have found evidence suggesting the presence of an unusual agent in that the CSF of certain patients shows the ability to kill human cells in tissue culture—there is evidence that this is due to a particle but it is not prevented by some common inhibitors of virus growth and there is no evidence that it is due to anything that can replicate in tissue culture.[1] However, CSF that produced such changes was injected intracerebrally into common marmosets and apparently produced a change in their behaviour which was clearly seen after eighteen months as they became less active in general and incidentally had produced less offspring. The same agent has been found in the CSF of patients with severe neurologic syndromes of obscure origin. At this stage all one can say is that some new possibilities have opened up but many further experiments are needed employing a wide variety of techniques and with a high degree of expertise on all sides, psychiatric, pathological, behavioural, and virological. I am reminded that the first experiment that indicated that a virus might cause colds was done in 1914, and yet cold viruses were not cultivated until over 40 years later. No doubt virology has advanced a great deal since then but substantial advances in ideas or techniques still take time to achieve. I think we need to be industrious and effective but not expect to have things sorted out for decades.

It is also possible that other diseases are due to infections or much modified by them. Rubella virus can be found in the joints of those who develop arthritis after infection with that virus. I can also mention a few studies made at the Clinical Research

1. Crow, T. J., Tyrrell, D. A. J., Baker, H. F., Bloxham, C., Davies, H., Ferrier, I. N., Johnstone, E. C., Parry, R. P., and Ridley, R. M. 'Detection of a "virus-like agent" in CSF in patients with schizophrenia, affective psychoses, Huntington's chorea and some neurological conditions and attempts to demonstrate its transmission', *Biological Psychiatry*, Perris, C., Struwe, G., and Jansson, B. (eds) (1981) p. 59.

Centre. We know that one form of arthritis SARA can follow non-specific urethritis due to chlamydiae and probably ureaplasmas. Dr Denman's group have evidence suggesting that circulating lymphocytes in patients with Behcet's disease and joint lymphocytes from patients with rheumatoid arthritis resist infection with a herpes virus, which may mean they are carrying it in a non-infectious form. This need not be the only relationship with arthritis—a recent study has shown that exacerbations in Juvenile Chronic Arthritis (Still's Disease) follows after infections with rhinoviruses or streptococcus pyogenes. It seems to me that with a new generation of techniques further work may well bear further fruit.

If it should turn out that viruses are involved in the causation of mental or nervous diseases then this fact would open new lines for investigating and treating such conditions. A new virus might be found, or perhaps one we had seen somewhere else, for instance, in the intestinal tract, but could not culture or understand. Such a discovery would not deny the significance of the effects of genetics, early experience, or drug treatment on the disease process. However, it might well take us nearer to the prime cause for nerve cell damage and disorder and if antiviral treatment makes progress we might even develop a radical treatment that halted the fundamental disease process. However, research in a field like this is bound to be difficult for years to come. There are now a few experimental results which seem to be valid and repeatable but much is still uncertain and no settled conclusions are going to be possible for some time to come. It is my impression that in the end infection may well be found to play a role in a number of chronic diseases the ultimate cause of which is at present unknown.

6

Dangerous work with microbes

'GENETIC ENGINEERING'

Pasteur said 'It is characteristic of science and discovery that they continually open new vistas to our view.' For today's biologist this is particularly true of the concatenation of new techniques often called genetic manipulation or genetic engineering.

Some of them had become familiar to the virologist—techniques to separate nucleic acids, split them with specific endonuclease enzymes, and map and eventually sequence them, replicate or copy them *in vitro* with suitable enzymes. However, other techniques were developed whereby plasmids carrying antibodic resistance genes could be inserted into bacteria at will; furthermore, lengths of foreign nucleic acid could be inserted with them and be replicated along with the rest of the plasmid as the bacteria grew and divided. Finally, by ensuring that the nucleic acid was inserted with appropriate sequences preceding it, it could be translated and the resulting gene product would accumulate in the bacterium and could, in due course, be harvested and purified.[1]

When this remarkable technical package was finally put together there were cries of alarm from those who had done it and others who had only vague ideas of what they were doing. It is unfortunate too that at first the group did not contain any who had been used to working with pathogenic organisms and had experience of how they are contained. On the other hand the problems of genetic engineering were different from those of handling pathogens. Basically it was feared that the organisms into which the foreign genetic information had been inserted might escape, invade the environment, including animals, plants, etc. and produceh armful products, perhaps pouring out toxins or hormones, or might be much more pathogenic than they were

1. Paul, J. 'Genetic engineering in medicine', *Hospital Update*, 8 (1982) p. 391.

prior to genetic manipulation. However, once a few more facts were available and the conclusions from them were agreed it became clear that the possibilities were not so hair-raising as had seemed at first. For one thing it was possible to produce bacteria for the work which could survive to a very limited extent in the environment or in the bodies of man or animals. For another most of the DNA that was to be cloned was unlikely to do any harm, either in itself or through its product. Even when genes or pathogens were being cloned it was realized that virulence genes are rarely effective on their own, but usually confer virulence only in the presence of a rather specific grouping of other genes in a particular strain of organism. On the other hand the gene for a toxin might well be as dangerous as the toxin producing organism itself. The conclusions have been that so-called 'shotgun' experiments in which all the genes of an organism are being cloned and in work with genes of dangerous organisms very strict containment is needed but for other work containment rather like that ordinarily used by microbiologists is appropriate. Worries and regulations about containment really did hold up progress for a time, but on the whole most workers now seem to be able to get access to containment facilities when they need them and rapid progress is being made.

The methods are proving enormously powerful in unravelling the genes of viruses as well as higher organisms. A DNA copy of an RNA virus genome can be made, cloned, and produced in large amounts for analysis and sequencing. This nucleic acid sequence can be used to deduce the amino acid sequence of the specified protein, provided a small amount of information about it is available. In this way, for instance, sequences of antigens from hepatitis B and foot-and-mouth disease viruses have been obtained. It has also been possible to get bacteria to synthesize the corresponding virus polypeptide. The synthesis is, however, imperfect in this case because the bacterium does not have the enzyme systems for glycosylating the peptide at the appropriate sites. In order to achieve this, special vectors have been constructed using, for instance, SV40 virus (a small single stranded DNA virus of simian cells) and these can be inserted into tissue cultures of such cells, which then translate large amounts of virus haemagglutinin

which can be glycosylated in the normal way and which, in fact, becomes inserted into the cell membrane, much as it would if the cell was infected with an influenza virus. In the end this might lead to alternative ways of making viral antigens.

For me, there are two even more fascinating consequences of

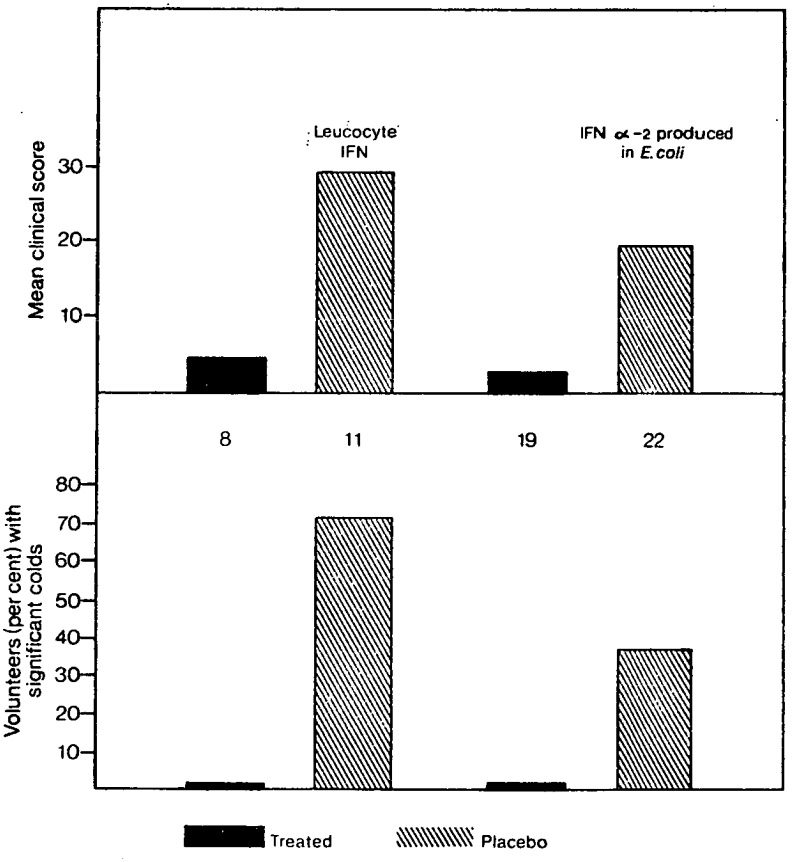

Figure 6.1. Results of administering highly purified human interferons as repeated intranasal spray to volunteers at the Common Cold Unit, Salisbury. The day after interferon sprays began they received nasal drops containing rhinovirus type 9. The clinical response to the virus was greatly reduced and the reductions are statistically significant. The numbers of volunteers in each group are shown between the panels. Data supplied by R. J. Phillpotts.

this work. One is that interferons have been studied in detail.[1] It was known by conventional experiments that there were three broad classes of interferons (IFN) namely IFN α, or leucocyte interferon, IFN β or fibroblast interferon and IFN γ or immune interferon, the first two being produced in response to virus infections and the last by lymphocytes responding to antigens or mitogens. Study of cloned DNA has shown that there are over a dozen human IFN α genes, but probably only one IFN β gene. The sequences are different but related. IFN γ, an immune interferon, is quite different, even the pattern of the gene is distinctive in that it has 'introns' or untranslated sections of the DNA strand. Having produced and characterized the DNA it has proved possible to obtain translated peptides for study. IFN α 2 is now being produced in large amounts in bacterial cultures. Thus, having waited ten years knowing that in principle interferon will prevent colds we can now undertake a series of experiments to develop this because at last sufficient material is available (fig. 6.1).

A second fascinating consequence concerns the development of synthetic antigens. It now becomes possible to examine the structure of the virus peptide by deducing the amino acid sequence, and with computer assistance constructing a model in three dimensions of the whole molecule. From this model likely antigenic sites may be picked out, for instance, a surface protrusion. The amino acid sequence can then be synthesized and used to immunize animals. Proceeding in this way an octapeptide

1. Weissmann, C., Nagata, S., Boll, W., Fountoulakis, M., Fujisawa, A., Fujisawa, J-I. Haynes, J., Henco, K., Mantei, N., Ragg, H., Schein, C., Schmid, J., Shaw, G., Streuli, M., Taira, H., Todokoro, K., and Weidle, U. 'Structure and expression of human IFN α genes', *Phil. Trans. R. Soc. Lond. B*, (1982).

FIGURE 6.2. The nucleotide sequence of cloned genes for two types of human α interferon, IFN α-1 (Hif-2h) and IFN α-2 (Hif-SN206) and the amino acid sequences of the peptides for which they code. Differences in the nucleotides and amino acids are marked by bars, and the dashes are introduced so that the sequence can be aligned as far as possible. Adapted from Figure 4 of Weissmann, C., Nagata, S., Boll, W., Fountoulakis, M., Fujisawa, A., Fujisawa, J-I., Haynes, J., Henco, K., Mantei, N., Ragg, H., Schein, C., Schmid, J., Shaw, G., Streuli, M., Taira, H., Todokoro, K., and Weidle, U. 'Structure and expression of human IFN α genes', *Phil. Trans. R. Soc. Lond. B* (1982).

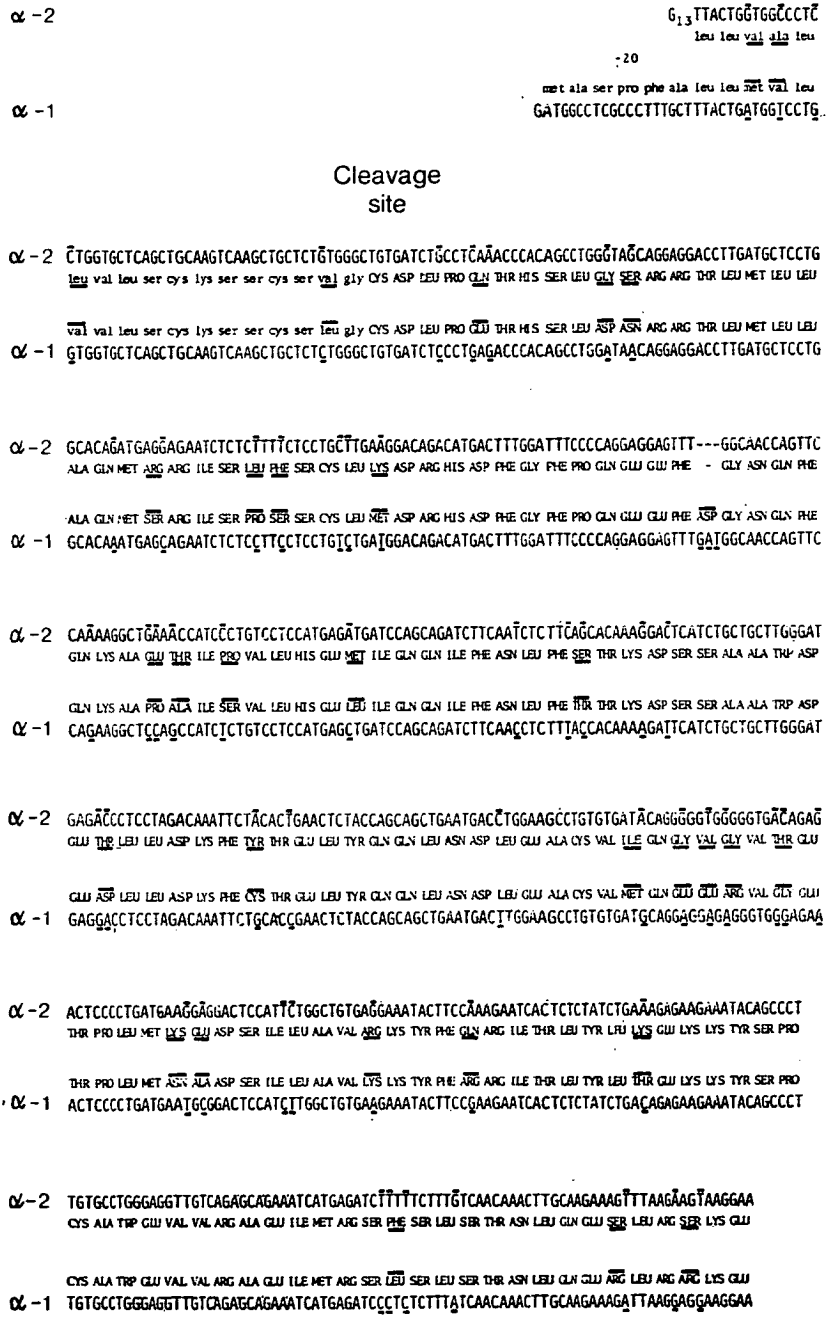
α -2
leu leu val ala leu
-20
met ala ser pro phe ala leu leu met val leu
α -1
Cleavage site
α -2
leu val leu ser cys lys ser ser cys ser val gly CYS ASP LEU PRO GLN THR HIS SER LEU GLY SER ARG ARG THR LEU MET LEU LEU
val val leu ser cys lys ser ser cys ser leu gly CYS ASP LEU PRO GLU THR HIS SER LEU ASP ASN ARG ARG THR LEU MET LEU LEU
α -1
α -2
ALA GLN MET ARG ARG ILE SER LEU PHE SER CYS LEU LYS ASP ARG HIS ASP PHE GLY PHE PRO GLN GLU GLU PHE - GLY ASN GLN PHE
ALA GLN MET SER ARG ILE SER PRO SER SER CYS LEU MET ASP ARG HIS ASP PHE GLY PHE PRO GLN GLU GLU PHE ASP GLY ASN GLN PHE
α -1
α -2
GLN LYS ALA GLU THR ILE PRO VAL LEU HIS GLU MET ILE GLN GLN ILE PHE ASN LEU PHE SER THR LYS ASP SER SER ALA ALA TRP ASP
GLN LYS ALA PRO ALA ILE SER VAL LEU HIS GLU LEU ILE GLN GLN ILE PHE ASN LEU PHE THR THR LYS ASP SER SER ALA ALA TRP ASP
α -1
α -2
GLU THR LEU LEU ASP LYS PHE TYR THR GLU LEU TYR GLN GLN LEU ASN ASP LEU GLU ALA CYS VAL ILE GLN GLY VAL GLY VAL THR GLU
GLU ASP LEU LEU ASP LYS PHE CYS THR GLU LEU TYR GLN GLN LEU ASN ASP LEU GLU ALA CYS VAL MET GLN GLU GLU ARG VAL GLY GLU
α -1
α -2
THR PRO LEU MET LYS GLU ASP SER ILE LEU ALA VAL ARG LYS TYR PHE GLN ARG ILE THR LEU TYR LEU LYS GLU LYS LYS TYR SER PRO
THR PRO LEU MET ASN ALA ASP SER ILE LEU ALA VAL LYS LYS TYR PHE ARG ARG ILE THR LEU TYR LEU THR GLU LYS LYS TYR SER PRO
α -1
α-2
CYS ALA TRP GLU VAL VAL ARG ALA GLU ILE MET ARG SER PHE SER LEU SER THR ASN LEU GLN GLU SER LEU ARG SER LYS GLU
CYS ALA TRP GLU VAL VAL ARG ALA GLU ILE MET ARG SER LEU SER LEU SER THR ASN LEU GLN GLU ARG LEU ARG ARG LYS GLU
α -1

FIGURE 6.2

which stimulates antibody against hepatitis B virus was produced. Recently by comparing sequences of 3 different foot-and-mouth disease serotypes,[1] the variable and therefore the probable antigenic sections of the molecule were picked out. These were synthesized and one not only stimulated serotype specific antibody but did it in such a way that the injected animals were protected against infection with virulent virus and did not die. Thus, contrary to many expectations, it now seems that we may be able one day to make vaccines with a few amino acids instead of a whole virus. This is quite plausible since a number of the antigenic determinants in carbohydrate antigens have been defined and are known to be determined by only a few sugar residues. However, from other viewpoints it is rather unexpected since the tertiary structure of virus peptides often seem to be unstable and may be lost when they are extracted from the virus particle. One felt, therefore, that when only a part of the peptide sequence was used there would be further losses of antigenicity. There are still important problems to solve in how to present the antigen to make it immunogenic. In the work with foot-and-mouth disease virus the peptide was linked to Key Hole Limpet haemocyanin and combined with aluminium hydroxide. It would probably not be acceptable to inject an antigenic foreign protein like this as part of a human vaccine, though it might well be all right if it were to be used in animals. However, oligopeptides have been made antigenic by combining them with plastics and in other ways and further work is clearly needed. We really don't yet know what it is about the size, shape, charge, or other features of the associated molecule that makes the whole a stimulus to an immunocyte. However, our knowledge of the handling of antigens is increasing all the time and it may well be that a step forward in molecular immunology will suddenly present us with a rational and effective way of applying these new results.

As another aspect of 'genetic engineering' techniques have been developed for making monoclonal antibodies by fusing antibody producing cells, particularly from mice, with tumour cells. These

1. Bittle, J. L., Houghton, R. A., Alexander, H., Shinnick, T. M., Sutcliffe, J. G., Lerner, R. A., Rowlands, P. J., and Brown, F. 'Protection against foot-and-mouth disease by immunization with a chemically synthesised peptide predicted from the viral nucleotide sequence', *Nature*, 298 (1982) p. 30.

hybridomas each produce one single species of immunoglobulin molecules which are very specific and reproducible reagents for identifying specific antigenic sites. They have already yielded valuable new information showing, for instance, that there are differences in the antigens of different rabies viruses and they are already being used as diagnostic reagents.

I must admit that I have been surprised at the speed with which novel results have been obtained with all these new techniques. But I do not mind being wrong about the time-scale as I am relieved to discover I was right as a member of the Williams Committee to say that genetic manipulation should be encouraged to proceed, using safeguards, since it offered significant possible advances for medicine, and particularly infectious diseases, as well as in many other fields.

MICROBIAL SAFETY

There has been progress in improving safety at work in most industries in recent decades but there has been increased anxiety among some groups on the safety of those working with pathogenic organisms. This has been reflected in the newspapers as well as in professional and scientific publications. A number of factors have lead to this situation. One is the background of disease in the community. Not so long ago smallpox was endemic in many countries, was imported periodically into Britain and a substantial proportion of the public was vaccinated at birth and re-vaccinated later in life especially if they travelled abroad. Then vaccination declined and has now been abandoned as a general public health policy and as a result fewer and fewer individuals have any sort of immunity. Thus, although the viruses have not changed—variola major has a mortality of about 20 per cent and variola minor less than 1 per cent—the environment and social attitudes have. This is particularly so since two incidents, one in London and one in Birmingham, in which virus escaped from a research laboratory and caused cases and deaths though, thanks to good public health measures, no general epidemic developed. Nevertheless it is unacceptable that a virus escaped and that anyone died. One response would be to destroy all smallpox viruses

held anywhere. But we need to keep the viruses in laboratories and maintain the ability to handle and identify them, in case a new smallpox-like disease appears, perhaps as a mutant derived from an animal pox virus. Nevertheless, the risks must be kept to a minimum. WHO has therefore suggested that the virus be held in only a few laboratories and be destroyed in the rest and they and the national authorities agree that live virus will be handled only under the highest degree of containment.

However, there are many lesser pathogens which still represent real risks to those who handle them. For instance, it was demonstrated that workers who handled *M. tuberculosis* without proper facilities for preventing aerosol inhalation were at an enhanced risk of getting infected—this might include those doing post-mortems and those doing diagnostic tests on sputum specimens.

The situation has become more difficult because it is difficult to resolve it on a scientific basis. For one thing, trades-unions, in particular the ASTMS, which has an honourable record, in my experience, of having members who actively co-operate in efforts to increase safety in laboratories, have taken an active part in the debate. They tend to adopt an attitude of confronting and mistrusting the employers, who though committed to encouraging safe working are understandably cautious about allocating money for such purposes unless they can be sure they will be producing a real effect on a real problem.

In order to resolve these problems several committees have been appointed in the past. This is not the place to outline their working but the objective was to gather together experts and to get them to allocate organisms to classes indicating how dangerous they were and what methods should be used when handling them. However, various difficulties were encountered. For one thing, since there is an enormous variety of organisms it was very difficult to have a simple classification without some rather anomalous results; there were few explicit criteria for allocating or reallocating an organism though the groups drew on a great deal of personal experience, for instance that an experienced microbiologist could report that he had worked with agent X under condition Y for Z years and never found a laboratory infection. When there were disagreements one could only weigh the number of experts

on each side. My wish would be to increase the rational element in the argument by introducing specific and quantitative data whenever possible. This might include proper epidemiological surveys of the frequency with which various classes of individuals experience various infections—to demonstrate and, if possible, measure any increased risk attached to laboratory work, as compared perhaps with exposure from contact with patients. As another type of measurement it should be possible to estimate in quantitative terms the degree of protection provided by the precautions advocated by the various experts and to resolve disagreements by reference to the amount of protection offered rather than by personal preferences for particular techniques or types of equipment. Then we move into a more difficult field; it would be desirable to know the infectious dose of agents for man by various routes of exposure; it seems important to consider the relative significance of different routes of infection. A great deal of interest has, in recent years, been concentrated on controlling aerosols, though contaminated hands are probably still a most important vehicle for transferring infection. Admittedly quantitative data are difficult to come by but it is clear that while influenza is probably harmless on the fingers it is not when inhaled, whereas enteric bacteria may be pathogenic if only a few are swallowed and arboviruses are probably particularly dangerous if pricked through the skin. It is still difficult to relate fragmentary information about the infectious dose of pathogens for man to the probability of a particular degree of exposure in a particular laboratory giving rise to an infection. For one thing dose—response curves are usually very 'flat' so doubling the number of organisms to which a subject is exposed produces much less than a doubling of the frequency of infection. Ultimately the only secure conclusions will be those based on epidemiological-type studies but in order to apply them as widely and as intelligently as possible we need to consider all the other types of information available.

This is all hard enough but even if we can work out how likely it is for a laboratory worker to be infected we still need to take account of the 'nastiness' of the disease, the effect of any vaccination or treatment available, the propensity of an epidemic to

develop, the state of immunity in the population, and the attitude of society to the occurrence of such infection. Clearly there must remain a great deal of personal judgement in deciding what to do but it seems important to make that judgement as informed as possible and to be as explicit as possible about what facts have been used in reaching the judgement. It is also plain that there will have to be a continuing process of reassessment, as new pathogens are discovered and new facts about the properties of old pathogens and their treatment become available. There are also likely to be new ideas and facts on the effectiveness of various methods of containment. It will always be difficult in those many instances where total containment is not needed, to find a degree of containment the inconvenience and expense of which is in reasonable balance with the extent to which it reduces the risks of infection. That word 'reasonable' may solve the problem of drafting a regulation, but it still leaves a great deal of hard thinking for those who make decisions and it conceals the fact that quite often complete agreement is impossible, even when there is goodwill on both sides, which unfortunately in this field is not always the case.

In summary, although there are unresolved differences about what to do to provide safe working with pathogenic organisms there is no need to fear that public health is at any risk from their being used in diagnosis, research, and manufacturing laboratories, and without such uses patients could not be diagnosed and given specific treatment, advances in this field could not be made, and necessary materials for treatment and prevention could not be provided. There are serious gaps in our knowledge about which organisms are a danger, how effective our controls really are, and disagreement about how far we wish to reduce risks. It should be possible to use present information and previous experience and practice to get a rational and agreed system which can then be improved and refined as new information is provided either from unplanned incidents or systematic research.

7

Organization and training

STRATEGIES FOR THE CONTROL OF INFECTIOUS DISEASES

As we have stated earlier many infections are much less common than they used to be in countries like Britain so it is worth reviewing how we organize the prevention and treatment of infections.

It is perhaps understandable that such care is fragmented. For instance prophylactic vaccination, on which depends our control over diseases such as poliomyelitis and whooping-cough, is provided in infant welfare clinics, some run by clinical medical officers and others by general practitioners, organized in districts which may or may not follow schedules recommended centrally, or by vaccine manufacturers, or by local individuals. The work is partly done by local nursing staff. The proportion of children actually vaccinated varies enormously from area to area. Measles will probably be eliminated soon from the USA where almost all children are vaccinated but it still flourishes in Britain where barely a half of our children receive vaccine. This may well be due to the social attitudes in Britain, which place a high value on the individual being free from compulsion or near compulsion on health matters, but it must be partly due to the lack of effective organization and delivery of vaccination schemes. There have been local outbreaks of poliomyelitis and diphtheria because virulent organisms have been introduced into 'pockets' where vaccination rates have been low.

Transmission of infections is controlled in a number of ways. Housing regulations do generally avoid overcrowding but are probably not successful in the inner city area. Standards of food hygiene have been improved recently and refrigerators have become more common. Water supplies, even in rural areas are now almost all piped and of satisfactory bacteriological quality. The standards of sewage treatment have been raised in order to avoid pollution of rivers and shores and all this seems to decrease faecal-oral transmission of the enteric bacteria and hepatitis A

virus. However, it is not always realized that the pipe-work of some sewage collection systems is already reaching the end of its life. Some areas have already had to meet large bills to have them renewed and this may be a price others will have to pay to avoid water-borne or sewage epidemics in the future. We must beware lest we assume that enteric infections are no real problem simply because we have now reached a generally satisfactory level of control. Veterinary policy and inspection controls some of the zoonoses but there is still a steady input into the food supply of Salmonellas, particularly from poultry meat. Even school-children are taught the importance of cooking and storing frozen chickens properly but clearly not enough of the population know or apply this and infections continue. It is essential to reach high standards of kitchen hygiene if these are not to go on causing trouble.

Many major infections are treated in hospitals. Many of the old isolation or 'fever' hospitals have been closed down or reduced in size. This is sensible. But isolation facilities are still needed, preferably in single rooms in a general hospital. Strict barrier nursing techniques can prevent infection spreading to other patients and the infected patients get the benefit of the comprehensive diagnostic and therapeutic resources of a general hospital.

There is an unfortunate tendency to discount the use and value of isolation in general hospitals. This can be a nuisance when junior staff admit patients with open tuberculosis to general wards, thus producing unnecessarily large numbers of contacts who need to be followed-up with the worry and inconvenience that entails. On other occasions it can be more serious, as when children catch respiratory syncytial virus infections in the ward. In one study of a Canadian pediatric hospital it was reported that one-third of the cases of rotavirus infection detected there were contracted in the wards, and some of them were fatal. The frequency of surgical post-operative infections may be declining but they still occur and cause patients to spend millions of extra days in hospital. More effort is needed to reduce transmission in hospital. The results of diagnostic tests on patients both in hospital and in the community are assembled and analysed both locally and through the Public Health Laboratory Service (PHLS). The Communicable Disease

Surveillance Centre provides a weekly summary of laboratory confirmed infections for England and Wales and there is a similar publication for Scotland. The Department of Health also has staff who keep a special watch on infectious diseases from the centre of the organization, consider policy of vaccination, and so on. These give useful information on the appearance and disappearance of pathogens and on trends of incidence and local health authorities may take action if an undue incidence of some infection is recognized in their own district. The Medical Officer of Health, who used to be able to integrate many of the measures for preventing infection or controlling epidemics in a town or local area, disappeared during the reorganization of the Health Service, but many of the functions are carried on and will presumably have to be taken over by the new Health Districts.

Minor infections are self-treated or handled by GPs and here there is no great cause for satisfaction. Patients with colds still take expensive and sometimes useless forms of symptomatic treatment and may demand penicillin which is usually useless. Children with diarrhoea may be given antibacterial drugs or constipating mixtures which are undesirable. Their mothers receive insufficient information on oral hydration, so they may eventually need hospital therapy. We need to educate patients and medical staff about optimal management and to inculcate in both a little of that sense of confidence and wonder described by Lewis Thomas that the nature of their bodies is such that they can be expected to cope unaided with all the minor infections. All the same in the best practices, for instance those taking part in the reporting scheme of the Royal College of General Practitioners a serious effort is made to diagnose infections accurately and to handle them in the best possible way.

All medical graduates have received a substantial amount of teaching on the diagnosis and treatment of infections before they qualify though there is a mismatch between the time and importance attached to these and the proportion of the work of practice that they comprise—in the case of general practitioners perhaps one-third of clinical work arises from infections, mainly with respiratory viruses. Three-quarters of the cases in a 'walk in' pediatric clinic in Finland had acute respiratory infections. What-

ever other branch of clinical medicine is taken up graduates can expect to have to diagnose and treat infections and should be able to apply their basic training to that end—maybe to deal with a wound infection in the surgical ward, bacterial endocarditis in the cardiology ward, or pyelonephritis in the renal unit. But how well is this done? For instance, how well are antibiotics used in the average hospital? This is a problem that is rarely tackled, but in a recent study in a major London hospital it was found that a substantial proportion of patients were not handled in accordance with good modern practice, although most of the doctors responsible for their immediate care had just come through an undergraduate medical course. There are clinical attachments at infectious disease hospitals or units during these courses but in some schools the teaching is nominal and given at old and inaccessible departments. Nevertheless, there are, in principle, adequate facilities for the care of patients who, if more than mildly sick, will get medical attention and adequate chemotherapy or other forms of treatment.

In developing countries one can expect infectious diseases to decline in frequency as economic advance takes place, hygiene improves, and transmission is cut down; the severity may be reduced concomitantly by improvements in nutrition and general health. However, there may be a vicious circle effect, that infections such as recurrent diarrhoea and malaria may so impair an individual's vitality that he or she cannot summon up the energy to take any opportunities for socio-economic advance that are offered, so treatment of cases may break into that circle. On the other hand it is widely accepted that the best way to improve things is to provide basic preventive care. There is often an intellectual acceptance that 'prevention is the better part of cure' but there is no drama and little esteem from one's fellow doctors (and there are never any grateful patients!), in this type of work particularly if it is successful. In the developing countries efforts are concentrated in the mothers' and children's clinics and this is reasonable since the highest incidence of serious infections is in the children under five. It is now agreed that the proper approach is to give comprehensive care and not to rely on tackling a single problem with a single measure—this is illustrated by a study which

followed a group of children in West Africa who were protected from measles which, in that area, produces a high mortality often from secondary problems such as pneumonia and diarrhoea, but probably basically because the children are inadequately nourished. The study showed that vaccination had abolished the mortality from measles but that if the children were followed for a few more years their overall mortality was the same whether they were vaccinated or not. Indeed, success and confidence in improving nutrition and dealing with infection may have beneficial effects on acceptance and co-operating in family-planning work; once a mother is free of the fear that she will lose a young child she is much more willing to limit her fertility.

Some diseases like malaria and smallpox have been the objects of specific programmes, which aimed by a variety of measures, to treat all cases and to interrupt transmission. There are hopes that still other infections might be dealt with in this way, for instance, hepatitis B infection which is commonly carried by those living in the tropics and which is responsible for the high frequency of primary hepatoma in those areas, often the commonest form of malignant disease. However, some of these programmes have been seen to be failing recently.[1] This has even been reflected in what happens in Britain where the number of imported cases of malaria has risen noticeably in recent years. A lot of thought has been given to why this has happened. Some of the reasons are really administrative; the programme has not, in fact, been carried out as planned due to lack of resources or failures in execution. On the other hand programmes have also failed because they were not actually adequate to their purpose—for instance, mosquito control in some areas depended on insecticides to which the insects have acquired resistance, and dapsone resistance emerged and impaired the success of some leprosy control programmes. This must not detract from the fact that one disease has been eliminated from the face of the earth—namely smallpox. As mentioned elsewhere it was cleared from country after country by a combination of vaccination and case-finding and it was possible to do so because the disease occurs only in man, is readily detected and

1. Yekutiel, P. 'Lessons from the big eradication campaigns', *World Health Forum*, 2 (1981) p. 465.

spreads relatively slowly, and because a good vaccine is available. Furthermore sufficient funds and a dedicated staff were mobilized. Now many countries are reaping the benefits of giving up vaccination, which is not just a nuisance but has a small but significant mortality; international travel no longer needs vaccination certificates and so on.

Measles has some of the same characteristics as smallpox and now that cheaper and more stable vaccines are available it has been suggested that we should aim for worldwide eradication of measles. However, recent discussions show that even control of infections may be fraught with unforeseen problems and that eradication is very much more difficult to achieve on a worldwide scale than it is locally. The challenge and the difficulties are great but the objective is well worthwhile so it is to be hoped that where appropriate effective control programmes will be launched.

EDUCATION AND THE FUTURE

Those who have followed the text so far will realize that infection seems to me to be a common phenomenon and as our understanding increases we may find infectious processes to be involved in diseases which at present we think of as not infectious.

Looked at in the broadest biological context it seems that life began on this planet with organisms rather like our present day microbes. Higher plants and animals, both invertebrate and vertebrate, were then added to the primitive ecosystems. However, these ecosystems, no doubt much modified, are still a crucial part of life-cycles everywhere. Certainly soil-biology and digestion in ruminants and many other species depend on the presence of a vast array of micro-organisms. Man and animals will, therefore, always live surrounded by micro-organisms, though because of the wonderful adaptability of these organisms the exact species and how they survive and spread will change with circumstances. It is also true that many of these organisms are beneficial or at least harmless to vertebrates. Nevertheless it seems that in principle there are always bound to be some occasions on which the microbes harm men. As life changes infections will not disappear,

but will certainly change as the wild flowers change with the type of soil.

Thus man will always be living in balance with micro-organisms and from time-to-time the balance will be disturbed in favour of one invader or another. Certainly the pattern of infection has changed and will change but we can assume infectious illnesses will continue to occur and will require wise management. Of course, many aspects of general medicine contribute to that management, but I do not accept the quite common view that practice of infectious diseases is nothing but a small subdivision of general medicine and that any physician with general training knows all that is necessary to practice it. Assuredly there is a great deal of common ground just as there is between subjects such as cardiology and dermatology, but there are differences. (Any general physician should and would be able to handle a number of straightforward cardiological conditions but that does not prove there is no justification for a full speciality of cardiology.) There is firstly the need to have some individuals with extensive experience in diagnosing and handling patients with a wide variety of proved and suspected infections; secondly, the best practice and research in infectious diseases is based on a foundation of scientific knowledge that includes bacteriology, virology, and epidemiology on the one hand, and immunology and pathogenesis on the other, as well as a detailed understanding of the pharmokinetics, toxicology, and the antimicrobial range of a variety of antibiotics. It requires a substantial effort to build up such a foundation beyond that which is needed for the competent practice of a general physician or other specialist.

This surely justifies the recognition of infectious diseases as at least a sub-speciality. Without question though, it must be a different type of speciality from that in the past. The old type fever hospital wards are gone, we hope for ever, and practice needs to be in most flexible units with single-bed isolation and closely associated with a general hospital with a full array of resources for diagnosis and specialized treatment such as intensive care. The growth and influence of pediatrics means that those trained in general or adult medicine will rarely be allowed to care for children with infections and this is another argument for pro-

viding an infections unit in a general hospital. However, the practice of communicable diseases lacks something that many specialities have, namely skill at a specialized investigation—such as gastroscopy and attendant skills practised by gastroenterologists. In the USA many specialists also provide or supervise the diagnostic bacteriology or virology laboratory, but we know that this would not be tolerated in Britain and in any case would probably not be necessary. We are short of medical microbiologists but things should improve soon and we have only just over a score of infectious disease physicians. Conversely, applicants for clinical posts who had spent time in the laboratory would be unacceptable to selection committees. It has been suggested that there might be a special role in a District General Hospital for an infectious disease physician or a general physician with a special interest in the subject, to manage an isolation unit and the patients in it. Very little of this sort has actually been done, though such a unit, the Lister Unit, runs very successfully at Northwick Park Hospital. As an alternative, a hospital microbiologist might monitor and control the use of and effectiveness of the isolation facilities, but hospital consultants would be even less likely to give them care of patients either from outside or inside the hospital than they are with the present infectious disease physicians.

Thus, if infectious diseases are going to change but not disappear something should be done in medical schools before the present generation of fever hospital doctors retire and the subject is dropped from the curriculum. It amounts to demonstrating academic esteem by bringing younger doctors well trained in infection into the full activities of the teaching departments. These could be individuals trained in adult or pediatric medicine, a number would have worked in developing countries and have a scholarly and research interest in some aspect of infection in the broad way I have outlined. They should work in general hospitals (as well as in remote isolation wards) where students can meet them and their research can involve all relevant departments.

This renewal of academic esteem is, in my view, very important. For instance, a great deal of the recent revival of general practice was stimulated by the academic recognition it received, while the recent improvement in the calibre and training of

infectious disease physicians in the USA went hand-in-hand with the funding of academic sub-departments and the development of a first class journal, *The Journal of Infectious Diseases*. Other journals have been founded in recent years with similar emphasis, for instance *The Journal of Infection* and *The Journal of Hospital Infection* in the UK and *Infection* in Munich, as well as journals on antimicrobial chemotherapy. These might be regarded as the creations of a particular clique or interest group, but it is important to note that reports on infection figure quite prominently in general journals. Indeed, while writing this section I analysed the subjects of papers published in *The Lancet*, a journal with a high academic standard which covers all branches of medicine but which only accepts papers which seem to it to be of particular scientific or clinical importance. It is impressive to me how often the main theme of recently published papers was infection. Staff and students should realize that the study of infections is not a matter of past history or routine but an area of growing knowledge and interest.

SUBJECTS OF ARTICLES APPEARING IN *THE LANCET*
February to April 1982

Issues		12
Original articles and Preliminary Communications		82
Dealing with infections by:		
Bacteria	7	
Viruses	10	19 (23%)
Fungi	2	
Editorials		70
Dealing with infections		14 (20%)

8

Conclusion

The reader will know by now that this has not been a formal and systematic survey of the state of infection or of infectious diseases but the brief exposure of a collection of topics in that field that are interesting and important to me. Nevertheless, I hope they will not be discounted as idiosyncratic and of purely personal interest. Indeed, we need to remember that it was microbial species that colonized and prepared this planet for higher forms of life. Plants, insects, and vertebrates which are so easily seen, still depend totally on these far more numerous and invisible creatures for their continued existence. It is perhaps inevitable that of this great horde of organisms with which we are surrounded, on our skins, in our throats and bowels, as well as in soil and throughout our environment, some do from time-to-time cause us harm. They are so versatile and mutations are bound to occur so the situation cannot be static. Furthermore, we change ourselves and our environment so frequently and so radically that it is not surprising that age-old balances between us and them are disturbed. A proper perspective on infection is important for all.

As I was preparing this section I received journals indicating that things are, indeed, going the way I anticipate. In one, an article reported that by using new immunological techniques it was possible to show that pneumonia caught in the community around Nottingham was usually due to the pneumococcus but about one in ten cases were due to Legionella.[1] So we are continuing to learn more about the causes of our common infections, and these may be changing. Another journal presented what the authors called 'alarming' evidence that highly antibiotic resistant penicillinase-producing gonococci have become established in the UK and are beginning to spread within our population.[2] It is no use our protesting that it is not our fault and that the problem has

1. MacFarlane, J. T., Finch, R. G., Ward, M. J., and Macrae, A. D. 'Hospital study of community-acquired pneumonia', *Lancet*, 2 (1982) p. 255.

2. McCutchan, J. A., Adler, M. W., and Berrie, J. R. H. 'Penicillinase-producing neisseria gonorrhoeae in Great Britain 1977/81: alarming increase in incidence and recent development of endemic transmission', *British Medical Journal*, 285 (1982) p. 377.

arisen because of the misuse of antibiotics in other countries—it will not go away because its appearance has not been 'our fault'; it will have to be tackled here in some new way—new antibiotics, new vaccines, new mores. Further, just because we are part of one world it would not surprise me if penicillin resistant pneumococci found their way here. We might want to use vaccines which have already been developed in the USA, but we need to be preparing ourselves for decisions on their use and on alternative strategies. As we find ourselves able to treat a range of virus infections with new specific antiviral drugs we shall need all our skill and care to work out how to use them effectively and without doing harm—I am already bothered from time to time when I see how inappropriately some are being used.

As we have seen, the full understanding of an infection requires broad scholarship and the exercise of a number of disciplines, ranging from epidemiology to pharmacology. Only on such understanding can wise judgements be made—perhaps unexciting ones like 'so and so is making a lot of fuss about nothing,' as well as how to handle a difficult case or an epidemic. It is, therefore, disturbing that in the field of public health the effect of the reorganizations of the health service has been to diminish the esteem in which such understanding and judgements are held in favour of skill in social and organizational matters and epidemiology of non-infectious diseases. Indeed, I understand that since the demise of the Medical Officer of Health it can now happen that in a particular district there may be no one with more thorough training and experience in the subject than an environmental health officer—an erstwhile Sanitary Inspector. It is good that there are still Medical Officers of Environmental Health and that a few epidemiologists are being trained centrally through the Communicable Disease Surveillance Centre at Colindale, some of whom will, no doubt, replace the present cohort of infectious diseases experts in the DHSS. I am concerned lest because of our present need to save money someone will decide that infections have been dealt with and are now a thing of the past. No one is owed a living in any field of endeavour and I think changes should come. However, our present freedom from infection is only a reflection of a number of activities which we often take for

granted—but if we discontinue them, for instance, whooping-cough vaccination, the disease can and will return.

The real solution must lie, however, in improving the situation in medical schools and hospitals. There are some remarkable paradoxes there. It has been proposed and was, I believe, agreed that there should be physicians 'with an interest in' infectious diseases in general hospitals, yet though I have no statistics on the subject I am impressed by the fact that I practically never seem to meet or be introduced to one. Since infections occur most commonly in children, pediatricians look after many such cases, yet few of them acquire laboratory skill or expertise in any relevant subject and young people in training are, I understand, not advised to do research on infection. This is in marked contrast to the USA where some of the most important figures in increasing our understanding of infectious disease have been pediatricians by initial training, and often remained in departments of pediatrics for the rest of their careers. But this specialized knowledge should be acquired as part of the broadest possible training.

As I have indicated the proper course of action may embrace considerations of epidemiology in the community including clear thinking on subjects as emotive as promiscuous behaviour and sexual 'freedom'. Then again, the care of the individual patient is incomplete unless the patient receives not only proper investigation and treatment, but also considerate and humane treatment from a professional individual who knows he or she is a fellow human-being and wants to give personal help in what is usually a major event in his or her life. This is as true in the field of infectious disease as in any other branch of medicine. The reductionism of the scientific method is essential if we are to understand the problems of the patient's disease and how to solve them. The results must be applied in the context of a holism which sees the individual as a person, and more than the sum of his parts, and, for me, of unique and eternal significance.

Infections no longer plague us the way they did; individual infections may disappear from certain areas but infections as a whole cannot be abolished, they can only be held in check, and over much of the globe they have still to be reduced to a bearable low incidence. There is still much to do.