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1.1. Introduction

1984 marks the centenary of the first use of one of the most effective viral vaccines (rabies, Pasteur, 1884) as well as being the famous milestone of fictional political forecasting (Orwell, 1949). This 100 year period has witnessed the industrialization of countries throughout the world and, along with this social and economic development, marked changes in patterns of infectious disease both accompanying and in some cases caused by the population and social changes. Excellent examples of these medical changes are shown in Figs. 1.1–1.3, where mortality in different age groups is compared for the two years, 1910 and 1967 in Germany for infectious diseases, heart and circulation disease and neoplastic disease, respectively. A dramatic drop in mortality at all ages, but particularly in children, from infectious disease is noted between 1910 and 1967, whereas, conversely, an increase in mortality in older persons (but not children) is noted which is caused by heart and circulation diseases and neoplasms. Disease patterns are still changing today and new viral diseases are discovered regularly (witness the fevers of Marburg and Lassa in the last decade, and, more recently, the different viruses associated with AIDS). Indeed there is every reason to assume that continual change in infectious diseases is to be expected in the future. Even the arrival of potent antiviral compounds may not eradicate diseases such as herpes, but rather may alter the pathogenic process of the virus itself as strong selective pressures are brought to bear. A similar phenomenon has been happening with bacteria such as Staphylococci or Streptococci as, over the years, strong selective pressures exerted by antibiotics have led to the emergence of organisms with reduced or altered pathogenicity. In the case of malaria, wide-
spread use of antimalarials on the one hand has led to a gradual and threatening build up of drug resistant strains of parasite and also the use of DDT to destroy the mosquito has led to development of resistance in the vector. Therefore both eukaryotes and prokaryotes possess a dramatic ability to adapt to a changed environment, and viruses are no exception.

As bacteriologists before us have done, we should ask ourselves which viral dis-
Fig. 1.3. Age distribution of mortality in 1910 and 1967 for the Federal Republic of Germany: neoplasm.

eases are important causes of mortality and morbidity, and, amongst these which would be the most suitable for ultimate control or even eradication. In fact, the question is more complex than this because in different parts of the world different viral diseases are important and even the same virus (such as measles) may cause very different disease syndromes. Whilst in most major European countries respiratory viruses are an important cause of morbidity and mortality, in third world countries measles, polio and diarrhoeal diseases predominate in this respect. A potential for distorted programmes of control of viral disease may easily occur, with most research centred on developed countries and therefore oriented towards viral disease in those countries. An excellent example is in the area of antiviral chemotherapy. At the present time most research effort is undoubtedly in the area of herpes infections, particularly HSV-2 causing genital infections, and this is closely followed by the search for new compounds against influenza A virus and rhinoviruses. Also, although influenza A is a pandemic virus causing mortality and morbidity throughout the world the same cannot be said for herpes viruses. Although infections with herpes viruses are universal, the impact of these nevertheless pale into insignificance beside medical problems with measles, arboviruses and hepatitis A and B in third world countries. So the direction of research effort needs continuous reassessment but, more importantly, some international perspective and direction. The World Health Organisation has provided this perspective for the eradication of smallpox from the whole world and continues to provide direction with its integrated ‘Health for All by the year 2000’ programme (Fig. 1.4) which calls on member states to pursue a programme aimed at attainment by all people of the world, of a level of health that will permit them to live a socially and economically produc-
The programme includes sections on the control of certain viral diseases causing respiratory infection and diarrhoeal diseases. The WHO conference at Alma-Ata in the USSR in 1978 stressed the importance of primary health care: “essential health care must be based on practical scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the community through their full participation and at a cost that the community and the country can afford to maintain at every stage of their develop-
ment in the spirit of self reliance and self determination”.

This programme does not, at present, envisage eradication of any particular viral disease, as smallpox was eradicated, because this may not gain the necessary full support of all countries. Individual countries might, and are, considering ‘national’ eradication of certain virus infections such as measles in the USA, Cuba, Bahamas, Canada and Barbados where mortality rates of less than 1 measles death per 100,000 population have now been achieved. Polio is another example of a viral disease which can be eradicated nationally, but of course a ‘national’ eradication always means that re-introduction from outside can constantly occur.

1.2. Important viral diseases in third world countries

Table 1.1 illustrates illness and death caused by infectious diseases (viruses, bacteria and parasites) in Africa, Asia and Latin America. Viruses are the single chief cause of mortality, amounting to many millions of persons per year. Among these virus infections the worst culprits are respiratory viruses such as influenza, and measles and rotaviruses. Although an estimated 5–10 million persons die of enteric infections in these three continents each year, viruses will cause only a proportion of these cases and a similar situation will be true for respiratory illness. We shall examine the methods developed for the prevention of measles, influenza, polio and rotaviruses later on (Chapters 8, 7, 4 and 9, respectively) but it may be mentioned here that live polio vaccines used so successfully in industrialized countries are much more difficult to apply successfully in third world countries where problems of vaccine administration, heat lability control and viral interference become very important. Measles programmes are being initiated now in certain third world countries (reviewed by McKenzie, 1983), but vaccines against diarrhoeal diseases are in their infancy. Research has been orientated towards the development of successful inactivated or live vaccines or chemoprophylactic agents against influenza for the last 40 years with only limited success and even less success against other respiratory viruses such as respiratory syncytial virus and parainfluenza viruses.

Little emphasis is given in Table 1.1 to mortality from arboviruses other than dengue, and from hepatitis A and B viruses. A successful yellow fever vaccine was developed in the 1940s but is not used for mass immunization but rather for containment, whereas the development of vaccines or chemoprophylactic agents against hepatitis is only beginning and so far has only resulted in vaccines and drugs with a very limited use on a large scale because of the expense involved.

Rabies vaccine, on the other hand, and the topic of our introductory sentence has been a success story in developed and underdeveloped countries. Cheap and effective rabies vaccines have been produced locally, with the help of the network of Pasteur Institutes throughout the world, to contain this terrifying disease (Chapter 6).
### TABLE 1.1.
Estimates of illnesses and deaths associated with major infectious diseases of Africa, Asia, and Latin America, 1977–1978 (after Kapikian et al., 1980)

| Disease                        | No. of cases per year | No. of deaths per year |
|-------------------------------|-----------------------|------------------------|
| Diarrhoeas                    | 3–5 billion           | 5–10 million           |
| Respiratory illnesses         | Not estimated         | 4–5 million            |
| Malaria                       | 150 million           | 1.2 million            |
| Measles                       | 80 million            | 900 000                |
| Schistosomiasis               | 20 million            | 0.5–1 million          |
| Whooping cough                | 20 million            | 250 000–450 000        |
| Tuberculosis                  | 7 million             | 400 000                |
| Neonatal tetanus              | 120 000–180 000       | 100 000–150 000        |
| Diphtheria                    | 700 000–900 000       | 50 000–60 000          |
| Hookworm                      | 1.5 million           | 50 000–60 000          |
| South American trypanosomiasis| 1.2 million           | 60 000                 |
| Onchocerciasis skin disease   | 2–5 million           | low                    |
| River blindness               | 200 000–500 000       | 20 000–50 000          |
| Meningitis                    | 150 000               | 30 000                 |
| Amebiasis                     | 1.5 million           | 30 000                 |
| Ascariasis                    | 1 million             | 20 000                 |
| Poliomyelitis                 | 2 million             | 10 000–20 000          |
| Typhoid                       | 500 000               | 25 000                 |
| Leishmaniasis                 | 12 million            | 5000                   |
| African trypanosomiasis       | 10 000                | 5000                   |
| Leprosy                       | 12 million            | very low               |
| Trichuriasis                  | 100 000               | low                    |
| Filaria                        | 2–3 million           | low                    |
| Giardiasis                    | 500 000               | very low               |
| Dengue                        | 1–2 million           | 100                    |
| Malnutrition                  | not estimated         | 2 million              |

In general therefore we can conclude that certain viral diseases are ‘shared’ between developed and underdeveloped countries (such as influenza, measles, polio and rabies) and research and technical developments in industrialized nations will hopefully be applied worldwide. An important qualification here is that new vaccines and antivirals should not be too expensive and, unfortunately, recent rabies vaccines (Chapter 6) and hepatitis vaccines (Chapter 16) are extremely costly. Live attenuated polio and measles vaccines are produced very cheaply and with more attention to their delivery (Chapters 4 and 8) can and should result in a dramatic decrease of polio and measles in these countries in the next decade.
1.3. Important viral diseases in industrialized nations of the world

As we have emphasized above, deaths from infectious viral disease in industrialized nations and also in those third world countries with well organized social infrastructure (such as China in the last 30 years) have been steadily dropping over the last 100 years, although there is still a considerable scope for further reductions in many countries. Table 1.2 shows death rates from infectious diseases in countries with ‘fully developed health services’ compared to those without these facilities. Table 1.3 further emphasizes marked differences in mortality caused by acute respiratory infection (bacterial and viral) in children between a third world continent (Africa), the USA and Europe. Mortality is overall 10 times higher in Africa than in the USA but nearly 60 times higher in the 1–4 year olds. Also interesting is the two fold higher mortality in children in Europe compared to the USA, at least at the beginning of the 1970s.

To put mortality from infectious diseases into some perspective Table 1.4 shows mortality in the USA in June 1982 from all causes. Deaths from pneumonia and influenza, for example, list seventh in such an analysis. The incidence of viral dis-

TABLE 1.2.
Death rates from infectious diseases (per 100 000 per annum, 1974–5) (after Lambert, 1983)

|                      | Group A |                      | Group B |                      |
|----------------------|---------|----------------------|---------|----------------------|
|                      | 14 countries with fully | 4 countries in Central |         |
|                      | developed health service | and South America |         |
| Pneumonia, influenza,| 57.5    | 102.0                |
| bronchitis           |         |                      |
| Tuberculosis         | 4.1     | 13.7                 |
| Measles              | 0.1     | 3.6                  |
| Whooping cough       | 0.009   | 4.1                  |
| Tetanus              | 0.04    | 2.5                  |
| Poliomyelitis        | 0.003   | 0.3                  |

TABLE 1.3.
Mortality from acute respiratory infection in children 1970–73, rate/100 000 population

|          | Infants | 1–4 yrs | 5–14 yrs |
|----------|---------|---------|----------|
| Africa   | 1454    | 467     | 22       |
| N. America | 146 | 8.0     | 1.5      |
| Europe   | 390     | 15      | 2.1      |
| Total    | 762     | 101     | 8.4      |

*Pan American Health Organisation (1982)
TABLE 1.4.
Relationship between cause of death and death rate in the USA in 1982 (from MMI)

| Cause of morbidity or mortality | Estimated mortality June 1982 | Estimated number of physician contacts June 1982 |
|---------------------------------|-------------------------------|-----------------------------------------------|
|                                 | Number                        | Annual death rate/100 000                     |
| All causes (total)              | 157 164                       | 826.7                                         |
| Accidents and adverse effects   | 8251                          | 43.4                                          |
| Malignant neoplasms             | 35 512                        | 186.8                                         |
| Diseases of heart               | 58 630                        | 308.4                                         |
| Suicides, homicides             | 4011                          | 21.1                                          |
| Chronic liver disease and cirrhosis | 2110                      | 11.1                                          |
| Cerebrovascular diseases        | 12 091                        | 63.6                                          |
| Pneumonia and influenza         | 3555                          | 18.7                                          |
| Diabetes mellitus               | 2643                          | 13.9                                          |
| Chronic obstructive pulmonary diseases and allied conditions | 5114 | 26.9 |
| Prenatal care                   |                               |                                               |
| Infant mortality                | 3200                          | 10.6/1000 live births                         |
|                                 |                               |                                               |

TABLE 1.5.
Incidence of virus diseases in USA (1976) (after Lambert, 1983)

| Incidence of acute conditions ×10⁶ (%) |
|---------------------------------------|
| Upper respiratory disease             | 128 (27.7)                      |
| Influenza                             | 110 (23.9)                      |
| Common cold                           | 97 (21.0)                       |
| All acute conditions                  | 461 (100)                       |

In summary, therefore, in the industrialized and more wealthy nations of the world infectious diseases including viral diseases play a much reduced role in causing mortality but amongst the important viruses in this respect are particularly respiratory viruses such as influenza A and B, and respiratory syncytial virus. Pandemic influenza A virus, in addition, causes considerable morbidity and economic disruption.
TABLE 1.6.
Visits to physicians with diagnosis of viral infection in USA (1977) (after Lambert, 1983)

| Diagnosis                      | No. of visits $\times 10^6$ |
|-------------------------------|----------------------------|
| Acute urinary tract infection | 23.9                       |
| Influenza                     | 10.2                       |
| Common cold                   | 4.2                        |
| Herpes febrilis               | 1.3                        |
| Herpes zoster                 | 1.3                        |
| Varicella                     | 0.77                       |
| Infectious hepatitis          | 0.64                       |
| Other viral diseases          | 2.04                       |
| Total office visits           | 1114                       |

1.4. Disease syndromes caused by viruses

We have briefly mentioned above clinical diseases and syndromes such as influenza, respiratory tract infections, hepatitis, and arbovirus infections resulting from virus infections. But many of these disease syndromes may be caused by a multitude of viruses, making specific diagnosis without the aid of a laboratory impossible. Most antiviral agents discovered to date have a very restricted range of antiviral activity and so to use these in the field it will be necessary to identify particular viruses causing a clinical syndrome rapidly and precisely. Partly for this reason, methods of rapid virus diagnosis have been investigated rather intensively during the last few years and the advent of monoclonal antibodies, for example, should hasten this process. Meanwhile it will be useful here to briefly summarize the range of viruses responsible for these differing clinical syndromes, and finally to list the major viruses of man in a more logical 'scientific' manner, so that the reader will not end up completely confused!

1.5. Viruses causing respiratory diseases in humans

A very wide range of viruses ranging from the RNA-containing pleomorphic influenza viruses to the DNA icosahedral adenoviruses cause respiratory infection which may be completely indistinguishable by a clinician. Nevertheless some general observations are a useful guide, including the facts that rhinoviruses, ECHO viruses, reoviruses and coronaviruses rarely, if ever, cause lower respiratory tract infection but confine their attention to the upper respiratory tract and hence may often produce only mild respiratory illness (Table 1.7). Cytomegalovirus and varicella zoster, on the other hand, tend to produce only lower respiratory tract infections whereas influenza, measles, parainfluenza, RSV and adenovirus produce both. Finally, most
TABLE 1.7.
Viruses that cause respiratory disease in man

| Virus                  | Serotypes | Syndrome                                                                 |
|------------------------|-----------|--------------------------------------------------------------------------|
|                        | No.       | No. that cause resp. disease                                              |
| Adenovirus             | 38        | Pharyngitis, lower respiratory tract disease – infants, children, adults |
| Coronavirus            | 3         | Upper respiratory tract disease – all ages                                |
| Herpesvirus            |           |                                                                          |
| Simplex                | 2         | Stomatitis and pharyngitis – children, young adults                       |
| CMV                    | 1         | Pneumonia – young infants                                                |
| Influenza virus        | 3         | Influenza, pneumonia – adults; croup – children (Types A and B). Mild upper respiratory tract disease (Type C) |
| Paramyxovirus          | 5         | Croup, bronchitis, pneumonia – infants, children                          |
| Respiratory syncytial virus | 1     | Bronchiolitis, pneumonia – infants, children                              |
| Enterovirus            | 67        | Pharyngitis – children, adults                                            |
| Rhinovirus             | 150       | Upper respiratory tract disease – all ages                                |

(but not all) clinical cases of influenza are caused by influenza A and B viruses, whilst most cases of croup in infants are caused by RSV (Fig. 7.10 in Chapter 7).

1.6. Neurotropic and dermatological viral agents

Similarly, a wide range of viruses have a predilection for nervous tissue (Table 1.8). Some viruses such as rabies, polio and certain arboviruses target upon nerve cells, but in the case of most viruses central nervous system (CNS) effects result as an aftermath and complication of viral replication (e.g. mumps, herpes, rubella).

Certain of these disease syndromes in the CNS such as rabies can be identified by clinical examination of the patient, but even polio-like paralysis can be caused by other enteroviruses (Chapter 4). Certainly encephalitis following rash diseases such as rubella, mumps and measles presents few problems of diagnosis unless the person has been infected without a rash.
## TABLE 1.8.
Neurotropic and dermatropic viral agents

| Virus   | Species                        | Number of types associated with: | Main clinical syndrome               |
|---------|---------------------------------|----------------------------------|--------------------------------------|
|         |                                 | Total CNS disease Rashes         |                                      |
|         |                                 |                                  |                                      |
| Paramyx | Measles virus                   | 1 1 1                           | Measles                              |
|         | Mumps virus                     | 1 1 1                           | Mumps                                |
|         | Respiratory syncytial virus     | 1 1                             | Acute resp. tract disease            |
|         | Parainfluenza virus             | 5 3a                            | Acute resp. tract disease            |
| Picorna | Poliovirus                      | 3 3b                            | Poliomyelitis                        |
|         | Coxsackie virus                 | 30 16c 17d                      | CNS disease                          |
|         | Echovirus                       | 33 33a 20a                      | CNS disease                          |
| Herpes  | Herpes simplex virus            | 2a 2                            | Herpes                               |
|         | Cytomegalovirus                 | 1 1                              | Cytomegalic incl. disease            |
|         | Varicella-zoster virus          | 1 1                              | Varicella-zoster                     |
|         | Epstein-Barr virus              | 1 1                              | Infectious mononucleosis             |
| Arbo    | Alpha and Flavivirus            | 200 18b 8a                      | CNS disease                          |
| Pox     | Papovaviruses                   | 6 1i 5a                         | Papovaviruses                        |
| Other   | Rubellavirus                    | 1 1                              | Rubella                              |
|         | Lymph. choriomeningitis virus   | 1 1                              | CNS disease                          |
|         | Adenovirus                      | 33 5i 4a                        | Acute resp. tract disease            |
|         | SV40-like virus                 | 3 2a                            | Progressive multifocal leucoencephalopathy |
|         | Rabies                          | 1 1                              | Rabies                               |

*a Types 1–3.
*b Types 1–3.
*c Types A1, 2, 4–7, 9, 10, 14, 16 and B1–6.
*d Types A1–10, 16, 22 and B1–5.
*e All types.
*f Types 1–7, 9, 11, 13, 14, 16–19, 22, 25, 30, 32 and 33.
*g Types 1 and 2.
*h EEE, WEE, VEE, JBE, SLE, Ilheus, Looping-ill, Powassan, West Nile, etc., viruses.
*i Chikungunya, Dengue, West Nile, Sindbis, O’Nyong-Nyong, Colorado Tick Fever, etc., viruses.
+j Vaccinia virus.
+k Variola (now extinct), vaccinia, paravaccinia, orf, molluscum contagiosum viruses.
+l Types 1–3, 5 and 7.
+m Types 1–3, and 7.
+n JC and SV40-PML viruses.

### 1.7. Viruses causing rashes

Certain rashes in their typical form can be easily diagnosed as caused by the viruses of chickenpox (varicella zoster), measles or rubella (Table 1.9). However, diagnosis
TABLE 1.9.
Principal rashes in infectious virus disease in man

| Virus                        | Disease             | Features                                      |
|------------------------------|---------------------|-----------------------------------------------|
| Measles virus                | Measles             | Very characteristic maculopapular rash        |
| Rubella virus                | German measles      | Maculopapular rashes not distinguishable clinically |
| Echo viruses 4, 6, 9, 16     | Not distinguishable |                                               |
| Coxsackie viruses A9, 16, 23 |                     |                                               |
| Varicella-zoster virus       | Chickenpox/zoster   | Vesicular rashes                              |
| Variola virus                | Smallpox            | Vesicular rashes (Now extinct)                |
| Coxsackie A/16 virus         | Hand, foot and mouth disease |                                   |

of rashes caused by certain of the enteroviruses such as Echo 16 or Coxsackie A9 may be easily misdiagnosed as rubella. This would not be particularly important were it not for the propensity of rubella to cause foetal infections and abnormalities (congenital rubella syndrome).

1.8. Viruses infecting the foetus

Table 1.10 lists viruses which have been implicated in causing foetal abnormalities, abortion or postnatal infections. Undoubtedly the most significant and dramatic effects on the foetus are caused by rubella virus and the many and varied deleterious effects on the developing embryo have been encompassed as the ‘expanded rubella syndrome’ (Table 1.11). Infection of the mother in the first week of pregnancy may result in infection and sequelae in 90–100% of the foetuses (Chapter 9).

Herpes viruses (via infection of the cervix of the mother) may infect the foetus during delivery, whereas cytomegalovirus and vaccinia can infect the foetus in utero in the final trimester of pregnancy. Increased foetal deaths or abnormalities have been noted following infection of the mother with other viruses including polio, arboviruses, measles and influenza but these effects on the foetus are more likely to be caused via constitutional upset in the mother rather than by actual infection of the foetus or foetal tissue by the virus itself.

1.9. Viruses causing persistent infections

Most of the above mentioned viruses cause acute infection in humans following transmission from another person or from a vector such as a mosquito or other insects. But certain viruses can afterwards establish a latent or persistent infection
Viral infections during pregnancy implicated in foetal or neonatal disease

| Virus                          | Potential effect on mother | Potential effect on foetus or newborn |
|-------------------------------|---------------------------|--------------------------------------|
| Cytomegalovirus               | Usually asymptomatic, but sometimes moderate to high fever in primary infection | Chronic infection, congenital malformation, mental retardation |
| Echoviruses                   | Rubella-like illness, fever, aseptic meningitis | Fatal disseminated viral infection (hepatic necrosis) |
| Hepatitis A and hepatitis B   | Flu-like illness; chills and high fever, constitutional symptoms and jaundice, increased severity during pregnancy | Prematurity, foetal death, neonatal hepatitis vertical transmission of HBsAg |
| Herpes virus types 1 and 2    | Oral or genital infection probably more severe in pregnancy | Abortion, prematurity, fatal disseminated infection |
| Influenza                     | Increased mortality in pandemics | Increased foetal mortality |
| Measles (rubeola)             | No special effect | Probably increased foetal mortality |
| Poliomyelitis                 | Increased susceptibility, severity and mortality during pregnancy | Foetal death, neonatal poliomyelitis |
| Rubella                      | Often asymptomatic, or very mild illness | Foetal death, chronic persisting infection, congenital malformations |
| Varicella-zoster              | Often more severe, maternal death | Neonatal varicella, probably specific defects |
| Vaccinia and variola          | Increased severity and mortality | Foetal death, intrauterine neonatal smallpox or vaccinia |
| Venezuelan and western equine encephalomyelitides | Meningoencephalitis | Neonatal encephalitis |

in the patient, becoming dormant. This would by itself be of no particular consequence except for the fact that, unpredictably, certain of these viruses later become reactivated, causing a new clinical syndrome. An excellent example is shown by the herpes viruses (Table 1.12) which infect the ganglia and re-emerge, as in the case of herpes zoster or shingles a lifetime later. On re-emergence the virus can be transmitted to other persons and so the life cycle of a herpes virus can become very complex (Chapter 11). In the case of hepatitis B viruses the persistent shedding of virus into the blood stream also makes the ‘carrier’ a potential infector of others, via medical or dental equipment or blood transfusion.

Viruses which are able to persist form a troublesome group for prevention. Vaccines against herpesviruses are under evaluation at present but since reactivation
TABLE 1.1
Abnormalities in congenital rubella virus infections ('expanded rubella syndrome')

| Evident in neonatal period | May not be evident until months or years later |
|----------------------------|-----------------------------------------------|
| **Common**                 | **Rare**                                      |
| CNS                         | Encephalitis, enlarged anterior fontanelle     | Microcephaly                                 |
|                            | Mental retardation, language abnormalities,    |
|                            | motor deficits, autism                         |
| Eye                        | Pigmentary retinopathy, cataract, microphthalmia | Glaucoma, cloudy cornea, iris hypoplasia    |
|                            | Pigmentary retinopathy                        |
| Ear                        | Sensorineural deafness                        | Dermal erythropoiesis                        |
|                            | Sensorineural hearing deficits                |
| Skeleto-muscular           | Low birth weight, postnatal growth retardation, bone radiolucenties, micrognathia | Hepatostplenomegaly, thrombocytopenia, leukopenia, adenopathy |
|                            | Hepatitis, immunological dyscrasias, hemolytic anemia, hypoplastic anemia |
| Haematological             | Pulmonary arterial hypoplasia, patent ductus arteriosus, coarctation of aortic isthmus |
|                            | Septal defects, interstitial pneumonitis,     |
|                            | myocardial necrosis                           |

occurs in the presence of high levels of neutralizing antibody such vaccines may have little or no effect, unless they stimulate cell mediated immunity (Chapter 2). Similarly, antivirals are unlikely to eliminate latent herpes viruses from the ganglia and would merely hasten the healing of a particular reactivation episode.

1.10. Sexually transmitted diseases caused by viruses

Herpes simplex venereal infections are of considerable interest to the general public, virologists and antiviral chemotherapists and data from the USA appear to suggest infections of epidemic proportions (see Chapter 12). Data from the UK show a steady increase in HSV-2 genital infections but certainly not in epidemic proportions. Indeed it is most useful to place this virus in a context of other venereal infections. Recently published data from the UK would suggest that non-specific genital infections are increasing in incidence at least as rapidly as HSV infections. Although the aetiology of non-specific genital infection is still not fully elucidated, *Chlamydia*
### TABLE 1.2.
Examples of persistent viral infections

| Virus            | Site of persistence | Infectiousness of persistent virus | Consequence | Shedding of virus to exterior |
|------------------|---------------------|------------------------------------|-------------|------------------------------|
| Herpes simplex   | Dorsal root ganglia | –                                  | Activation, vesicles | +   |
|                  | Trigeminal ganglia  | –                                  |             |     |
| Varicella zoster | Dorsal root ganglia | –                                  | Activation, zoster | +   |
| EB virus         | Lymphoid tissue     | –                                  | Lymphoid tumour? | –   |
|                  |                     |                                    | (Burkitt’s lymphoma) |     |
| Cytomegalovirus  | Salivary glands     | +                                  | None known   | +   |
| Hepatitis B      | Liver (virus shed into blood) | + | Blood remains infectious |     |
| Adenoviruses     | Lymphoid tissue     | –                                  | None known   | ±   |
| Measles          | Brain               | ±                                  | Subacute subacute sclerosing pan-encephalitis |     |

*trachomatis* is recognized to be the commonest cause in Britain, and isolation rates from the cervix of unselected women attending sexually transmitted disease clinics in Britain may reach up to 31%.

Total new attendances at special (venereal disease) clinics in the United Kingdom rose by 4.6% in 1981 compared with 1980, continuing the increase noted each year since the early 1950s. This is less than the previous annual increase of 9% (which, however, was unusually large). The overall picture of sexually transmitted disease in British clinics in the past 30 years is one of the increasing importance of new cases requiring treatment in categories other than syphilis or gonorrhoea, which now account for only 16% of total cases requiring treatment. The largest absolute increase in new attendances by diagnostic category in 1981, apart from 'other conditions requiring treatment', was in non-specific genital infection: there were 132 391 new attendances, an increase of 6915 (5.5%) over those in 1980, but this was about half the previous annual rise of 11%. There were rises in most other diagnostic categories. The number of new attendances due to herpes simplex infection increased by 1300 (12.1%), those due to warts by 1700 (5.3%) and those due to candidiasis by 2894 (6%).

Other viruses including cytomegalovirus and hepatitis B virus are transmitted in semen from infected persons, but the general significance of this is not clear. HTLV-III has been implicated as a possible cause of acquired immunodeficiency syndrome (AIDS) in promiscuous homosexuals (see Chapter 14) and presumably transmission via person to person in semen might be a major factor.
1.11. Attempts at prevention of human viral diseases

Table 1.13 and Fig. 1.5 list, rather exhaustively (but not completely), a classification of viruses causing human disease, and Table 1.14 briefly summarizes information on currently used vaccines and chemoprophylactic agents against viral diseases. The epidemiology, strategy of replication and physical and antigenic structure of these viruses will be discussed as fully as possible in the ensuing chapters. However, a word of warning should be introduced here. DNA technology ('genetic engineering') techniques are being introduced very rapidly indeed and are expected to revolutionize the previously used biological approaches to development of new viral vaccines. The reader can safely assume that for most viruses discussed in the following chapters, even if it is not indicated in the text, that someone is cloning the particular gene into a eukaryote or prokaryote cell. It cannot be overemphasized that with both new vaccines and antivirals the initial discovery is often made by individuals and single groups. Only during later developments are the large teams of scientists required. Also, with antivirals, a new era has arrived which is seeing the first extended use in the clinic of inhibitory molecules against viral diseases, particularly herpes. So we shall undoubtedly see a plethora of new molecules each with certain biological and pharmacological advantages compared to the parent. Indeed, we are witnessing this trend already with molecular derivatives of acyclovir such as DHPG and DHBG (Chapter 11).

We have tried, in the ensuing chapters to present the reader with a review of the basic scientific knowledge and principles underlying development of vaccines and antivirals. New data should simply enhance interest in the topic and perhaps even encourage a reader to develop a vaccine or antiviral him or herself!

1.12. Economic costs of viral diseases

The impact of viral diseases on society can, to some extent, be expressed in economic terms and this again illustrates the magnitude of the infectious viral disease problem. In the USA, during the period 1972–1978, the annual mortality from influenza was 20000 deaths, the annual cost of treatment $300 million and the annual loss of productivity $750 million. The cost of less severe respiratory viral diseases, such as common cold occurring on the average more than twice yearly, is probably of the same magnitude. The distress and pain caused by recurrent labial and genital herpes infections is very large, and possibly increasing. The number of patients is difficult to express in economic terms, but an estimated number of 500 000 Americans are contracting genital herpes each year and approximately 100 million episodes of labial herpes will affect the USA population each year. The impact of gastrointestinal syndromes caused by viral infection can be illustrated by an annual mortality of 5–10 million due to rotavirus infections in children in Asia, Africa and South America.
TABLE 1.13.
Examples of viruses infecting humans

| Family         | Genus/Subfamily            | Example                                |
|----------------|----------------------------|----------------------------------------|
| Poxviridae     | Ortho pox                  | Smallpox virus                         |
|                | Para pox                   | Orf virus                              |
| Herpesviridae  | Alphaherpesvirinae         | Herpes simplex virus type 1,2          |
|                | Betaherpesvirinae          | Varicella zoster virus                  |
|                | ?                          | Cytomegalovirus                        |
|                | African swine fever group  | African swine fever virus              |
| Iridoviridae   |                            |                                        |
| Adenoviridae   | Mammalian adenoviruses     | Adenovirus type 2                      |
| Papovaviridae  | Papilloma virus            | Human papilloma virus                  |
|                | Polyoma virus              | BK virus                               |
| Paroviridae    | Parvovirus                 | Norwalk agent?                         |
| Reoviridae     | Reovirus                   | Reovirus type 1                        |
|                | Orbivirus                  | Colorado tick fever virus              |
|                | Rotavirus                  | Human rotavirus                        |
| Togaviridae    | Alphavirus                 | Eastern equine encephalitis virus      |
|                | Flavivirus                 | Yellow fever virus                     |
|                | Rubivirus                  | Rubella virus                          |
| Coronaviridae  | Coronavirus                | Human coronavirus                      |
| Paramyxoviridae| Paramyxovirus              | Parainfluenza virus 1                  |
|                | Morbillivirus              | Measles virus                          |
|                | Pneumovirus                | Respiratory syncytial virus            |
| Orthomyxovirida| Influenzavirus             | Influenza virus A                      |
| Rhabdoviridae  | Lyssavirus                 | Rabies virus                           |
| Bunyaviridae   | Bunyavirus                 | Bunyamwera virus                       |
|                | Phlebovirus                | Sandfly fever virus                    |
|                | Nairovirus                 | Crimean-Congo haemorrhagic fever virus |
|                | Uukuvirus                  | ?                                      |
| Arenaviridae   | Arenavirus                 | Lassa fever                            |
| Retroviridae   | Oncovirinae                | Human T-cell leukaemia virus           |
| Picornaviridae | Enterovirus                | Human foamy virus                      |
|                | Rhinovirus                 | Polio virus                            |
|                |                            | Human rhinovirus IA                    |
| Calciviridae   | Calcivirus?                | Norwalk virus?                         |
| Unclassified   |                            | Human rhinovirus IA                    |
|                |                            | Hepatitis B virus                      |
|                |                            | Marburg/Ebola virus                    |
|                |                            | Kuru                                   |
|                |                            | Creutzfeld-Jacob disease               |
|                |                            | AIDS                                   |
|                |                            | Delta agent                            |
|                |                            | Hepatitis nonA nonB virus              |

Many chronic conditions are initiated in infectious diseases. Hepatitis B may result in chronic infection in 10% of the cases, leading to chronic cirrhosis. An esti-
mated 150–200 million chronic carriers in the world poses a large medical problem. For some communicable diseases such as rabies, although the rate of morbidity is small or non-existent, nevertheless substantial costs are incurred in surveillance, prevention and health education. Also the costs for rabies extend into the agricultural sector of the community. With all communicable diseases allowance must be made for indirect costs such as production losses in the economy and these may sometimes amount to twice as much as the health service costs. Indirect costs again may spread over a number of sectors of the economy, including infected animal stock or food products etc.

1.13. Economic evaluation of programmes to control viral diseases

To date very few detailed studies have been undertaken to establish the cost and
| Virus                  | Disease spectrum          | Epidemiology/distribution | Antiviral agent               | Vaccine                          | Comments                                                                 |
|-----------------------|---------------------------|---------------------------|-------------------------------|---------------------------------|--------------------------------------------------------------------------|
| Influenza A           | Acute respiratory         | Pandemic virus            | Amantadine                    | Inactivated whole virus or split virus and subunit vaccines. Live attenuated vaccines (ca and ts mutants and host range mutants). | Both vaccines and amantadine have a comparable degree of efficacy (with 70% protection). Ribavirin aerosol trials unconfirmed at present. |
| Influenza B           | Mild respiratory          | Limited epidemics         | Interferon                    | As above                        | Antiviral agents required                                                |
| Influenza C           | Mild respiratory          | Not epidemic              | None                          | None                            | Antiviral agents required                                                |
| Parainfluenza viruses| Acute respiratory         | Children - world wide     | None                          | None                            | ts mutants under study. Early inactivated vaccines deleterious. Little work with antivirals at present. |
| Respiratory syncytial virus (RSV) | Acute respiratory      | Children - world wide     | Ribavirin                     | None                            | Early inactivated vaccine deleterious.                                  |
| Measles               | Rash and acute infection  | World wide                | None                          | Attenuated virus                | Successful vaccination programme in many countries. Early inactivated vaccines deleterious. |
| Mumps                 | Rash and acute infection  | World wide                | None                          | Attenuated virus                | Successful vaccine programmes in many countries                         |
| Coronavirus           | Mild respiratory          | World wide                | None                          | None                            | Ribavirin triacetate                                                    |
| Arenaviruses          | Acute generalised         | Tropical areas            | Ribavirin triacetate          | None                            | Ribavirin triacetate is under clinical investigation against Lassa virus. |
| Virus       | Disease spectrum                      | Epidemiology/distribution | Antiviral agent | Vaccine          | Comments                                                                 |
|------------|---------------------------------------|----------------------------|-----------------|-----------------|--------------------------------------------------------------------------|
| Togavirus  | Encephalitis, rash acute illness       | Almost worldwide           | None            | Attenuated (17D Yellow Fever) and inactivated viruses | Yellow Fever vaccine is effective. Vaccines against other viruses of the group are used on a small scale (e.g. TBE). |
| Rhabdovirus | Rabies                                 | Almost worldwide           | None            | Inactivated      | Effective new human diploid cell vaccine for immunization pre and post exposure. Range of other vaccines are effective. | Antivirals required for rhabdoviruses because the multiplicity of serotypes makes immunization improbable unless common antigenic determinants can be isolated. |
| Rhinoviruses | Common cold                            | World wide                 | Envir unconfirmed prophylactic activity versus rhinovirus interferon has mild prophylactic effect. | None            | None                                                                      |
| Poliovirus I, II, III | Enteric infections                   | World wide                 | None            | Effective live and inactivated Polio virus vaccines. | None                                                                      |
| Echo       | Conjunctivitis (enterovirus type 70), neurological disease (Polio) | World wide                 | None            | None            | None                                                                      |
| Coxsackie  | Warts                                 | World wide                 | None            | None            | None                                                                      |
| Papilloma viruses | Warts                                | World wide                 | None            | None            | Vaccines or antivirals required                                           |
| Virus                        | Disease spectrum | Epidemiology/distribution | Antiviral agent                  | Vaccine         | Comments                                                                 |
|-----------------------------|------------------|---------------------------|----------------------------------|----------------|--------------------------------------------------------------------------|
| Hepatitis A                 | Hepatitis        | World wide                | None                             | None            | Vaccines or antivirals required.                                         |
| Hepatitis B                 | Hepatitis        | World wide                | Ara-A + interferon               | Inactivated 'subunit' | Effective hepatitis B vaccine suitable for small 'at risk' groups. Interferon only active in some persons. Combined therapy a possibility. |
| Hepatitis non A non B       | Hepatitis        | World wide                | None                             | None            |                                                                              |
| Herpes viruses:             |                  |                           |                                  |                 | Vaccines may have limited usefulness because of virus latency and the complexity of immune responses. A number of effective antivirals are under trial. |
| HSV-2                       | Venereal         | World wide                | Acyclovir, Ara-A, BVDU, foscarnet, IDU (keratitis only), trifluothymidine (keratitis only), interferon | Experimental | |
| HSV-1                       | Superficial lesions (including venereal) | World wide                | As above                         | Experimental | |
| CMV                         |                   | World wide                | Foscarnet?                       | Experimental | |
| EBV                         | Encephalitis, keratitis, infections in immunocompromised persons | World wide                | None                             | None           | Mononucleosis                                                            |
| Herpes zoster               | Zoster, varicella | World wide                | Acyclovir                        | None            | Mononucleosis                                                            |
effectiveness of programmes for the prevention and treatment of viral diseases. Moreover, these have been concerned with vaccines and no work has been published as regards specific antivirals. However, the estimated cost to develop an antiviral agent is $20–100 million which, in relation to common diseases such as influenza and herpes, is economically acceptable but with less frequent viral diseases can be a problem for a private company. Such data as there are suggest that improved strategies of prevention of viral disease could make substantial savings and result in better health outcomes.

Some viral diseases such as measles and polio maintain high incidence levels unless immunization levels are constantly maintained, whereas others can be self eliminated when a threshold level of infection is reached. Where the incidence of a disease changes over time, established forms of treatment may lose their justification and should be phased out or altered.

The patterns of some viral diseases have changed due to medical intervention in another sphere and an example is the improvement in treatment of cancers and immunosuppression of transplant patients. This has resulted in an increasingly common situation where a successful, and often very expensive, treatment of a disease is threatened by opportunistic viral infections, mainly by latent herpes viruses. The cost of developing antiviral agents against these types of infections should be considered in the context of the total cost to manage these patients and the risk of an infection.

1.14. Benefit-risk and cost-effectiveness analysis of virus vaccines

An informal weighing of risks and benefits of immunization (e.g. for smallpox) has been carried out in some societies, like the UK, for hundreds of years. However, it is now possible to apply more precise scientific analysis to the problem. Such a scientific analysis of immunization benefits in the early 1960s led to a major alteration in national health policy in the USA — namely the decision that routine smallpox vaccination should be discontinued. The last case of variola minor in the USA was in 1949 and by 1963 the risk of death from all smallpox vaccinations was 1 per million for primary vaccinees, rising to 5 per million for children under 1 year of age. In addition, among primary vaccinees the combined rate of post vaccinia encephalitis and vaccinia necrosum was 6.5 per million for infants. On the other hand, the probability of a smallpox importation into the USA in 1970 was 1 importation every 12 years. It would probably have required 15 smallpox importations per year to produce the same mortality which was then associated with smallpox vaccination. This is an excellent example of the direct usefulness of statistics.

In the United States alone more than 50 types of vaccines, both bacterial and viral are used and one may question how worthwhile some of these vaccines are in economic terms. Cost effectiveness analysis and cost benefit analysis aggregate
the net medical care costs and net health benefits from a vaccination programme and thus help to give an economic analysis. Net medical care costs often include the cost of vaccine and its administration, cost of treating vaccine complications and the medical care savings due to prevention of disease. Net health benefits include reduction in morbidity and mortality. Also one may include the gains in productivity resulting from a reduction of absence at work. Other qualitative and more difficult to cost-estimate considerations must be included to place a vaccine programme in an accurate social and medical perspective e.g. pain and anguish of illness, compensation of victims of severe vaccine reactions etc. These days, quite necessarily so, political, social, economic and medical factors are all taken into account (or at least should be by national health authorities). It is an interesting and useful exercise to see how these analyses apply to 4 popular and seemingly useful viral vaccines (Willems and Sanders, 1981). The salient features of this analysis which mainly refers to experience in the USA (and therefore may differ in details in European countries, for example) are presented in Table 1.15.

The crucial issue for a vaccine strategy against rubella is the appropriate age of immunization. Prevention of congenital rubella syndrome is the aim of this programme, because rubella itself is a mild disease scarcely worth considering if it were not for the teratogenic properties of the virus. The teratogenic effect of the virus is unique in its selectivity of action and most embryos of mothers infected during the first trimester would be affected. As an example of the community effects in the 1964–1965 epidemic before vaccine was introduced, 5000 therapeutic abortions were carried out and 20 000 children were born with rubella syndrome in the USA alone. Also 2100 excess prenatal deaths were associated with the epidemic. Of the 20 000 children born with congenital rubella, 8000 were deaf, 3500 deaf and blind and several thousand suffered moderate to severe mental retardation. Estimated direct costs of the epidemic in the USA were $1 billion, mainly (90%) as regards long term care associated with rubella syndrome. In the USA after 1969, when vaccine became widely available, the strategy was to immunize all children as a routine, whereas adolescents and women of childbearing age were immunized selectively. In the UK, on the other hand, mainly school girls (not boys) were immunized. The basic strategy in the USA was to displace wild virulent rubella by attenuated non-teratogenic vaccine virus. A reduced objective was aimed for in the UK and the programme to date has not been so successful. In the USA, rubella epidemics have been prevented and cases of rubella have decreased continuously in the under 15 year age group. Most cases of rubella now occur among adolescents. A study of costs and benefits found positive net benefits. In 1972 the direct cost of acute rubella for 1 million persons was estimated at $2.7 million and the costs of congenital rubella syndrome in the offspring of 1 million unprotected females was $35.9 million. The benefit cost ratio for vaccine to 1 million females at 12 years of age was 25:1, assuming 100% immunization of the target population.

Since mumps vaccine was licensed in 1967 in the USA more than 40 million doses
TABLE 1.15.
Results of cost-effectiveness and cost-benefit analyses of some virus vaccines (from Willems and Sanders, 1981)

| Vaccine    | Efficacy | Duration of immunity | Unit of analysis | Vaccination cost per person | Net health effects                                                                 | Net medical care costs | Net costs including productivity gains |
|------------|----------|----------------------|------------------|-----------------------------|------------------------------------------------------------------------------------|------------------------|----------------------------------------|
| Poliomyelitis | 95%      | life                 | 1 million vaccinees | 0.81                        | Decrease in annual new cases of poliomyelitis (200) and annual deaths (1269)        | -0.2 million           | -0.9 million                           |
| Measles virus | 90%      | life                 | 1 million vaccinees | 3.0                         | Decrease in cases of measles (269 529), death (27), and cases of encephalitis (270) and retardation (90); increase in years of life (8061) | -4.6 million           | -11.3 million                          |
| Rubella virus | 95%      | life                 | 1 million cohort   | 3.0                         | Decrease in cases of acute rubella (72%) and congenital rubella (70%)                | -9.8 million           | -17.2 million                          |
| Influenza virus | 70%      | 1 year               | 1 million vaccinees | 3.0                         | Decrease in deaths (521) and increase in years of life (5423)                       | 2.7 million            | 1.7 million                           |

The additional costs and benefits are included.
have been used and the incidence of mumps has dropped from rates of 90–200 per 100,000 population to 7–10 per 100,000 in the late 1970s. It may be calculated that the use of mumps vaccine for a group of a million persons would prevent 74,000 cases of mumps and 3 deaths. Over a 30 year period mumps vaccine would reduce costs by over 86% and the benefit cost ratio approximates to 7:4:1. Mumps vaccine in Austria has a benefit cost ratio of 3.6:1 and in Switzerland 2.1:1 (data not shown in the table).

Comparable analyses appear to show that influenza vaccine is less effective in economic terms than rubella or measles vaccines but very different considerations pertain. The vaccine is recommended for special risk groups and not particularly for children. Medical care costs of vaccination during 1971–1978 totalled $808 million and 150 million persons were immunized in the USA, giving a cost of $63 per year of healthy life gained. Moreover, the cost effectiveness of vaccination improves with increasing age of the person vaccinated (because the highest mortality occurs in the over 55 year age groups) so that it costs $258 per vaccination for each year of healthy life gained in the under 3 age group, to $23 per vaccination in the 45–64 age group, to positive cost savings in the 65+ age group. Assuming influenza vaccine is 70% effective, vaccinating a million elderly persons would result in 5400 additional years of life at a net cost of $491 per year of life gained. Most people would agree that this is a reasonable use of medical resources.

Four million cases of measles occurred in the USA each year before vaccine was introduced in 1963, with 4000 cases of encephalitis and 400–500 deaths each year. Net benefits of measles immunization between 1963 and 1972 include savings of 1.4 million hospital days, 75 million school days and 7900 cases of mental retardation. The benefit cost ratio was approximately 10:1. In Finland, as an example of a European country, the benefit cost ratio was 3.7:1. However, as measles declines, marginal reductions in incidence will become increasingly costly. Measles will probably be eliminated as an endemic disease in the USA during 1984.

An excellent recent example of the application of cost effectiveness of viral vaccines is being carried out in several countries at the present moment with the advent of an effective vaccine against hepatitis B (HBV) virus (Szmuness et al., 1981). The vaccine is rather costly because of the technical problems of purifying and inactivating antigen from human sera ($140 per course of 3 doses of vaccine) and, more important, its availability may be limited in the near future. Therefore ‘decision analysis’ can be used to estimate likely costs and benefits of different immunization approaches in different populations at risk. A decision analysis model was constructed to compare 3 alternatives for prevention, which were:

a. immunizing all persons with no prior screening for indication of previous infection
b. screening all persons for indications of previous infection and then immunizing only those sero or antigen negative persons
c. passive immunization of persons exposed to HBV.
The estimated cost per person of hepatitis vaccination in a 5 year period in a homosexual population with a 60% prevalence of HBV markers and 15% annual attack rate without screening and vaccinations is $96.66. Vaccination of all persons in this group would result in a lowering of HBV incidence from 23 to 4%, costing $105.12 per person. However, screening followed by immunization would cost only $66.35 (because fewer people would be immunized). In contrast, for a group of hospital employees with relatively high exposure (0.5%) and annual attack rate of 6%, vaccination without screening is the lowest cost strategy ($104.22). For a low risk population (0.1% annual attack rate) neither vaccination nor screening followed by vaccination would result in a saving in medical care costs. Indeed the net medical costs per case of hepatitis prevented by vaccinating the latter population would be $22,469. In contrast, net medical care costs per case prevented are negative when the attack rate is greater than 5.6%. A very important caveat of the above discussion, however, is the fact that indirect costs saved by immunization, such as loss of productivity etc, are not included. If one is only interested in medical care savings then HBV vaccination should be carried out before or early during a period of unavoidable high risk as with surgical registrars, new dialysis unit patients and staff members, new prisoners, newly institutionalized mentally retarded patients, and promiscuous homosexuals.

We should note that in the example given above, which is rather USA-orientated, extrapolation to conditions in Europe may be questionable. In fact an excellent example of these differences has been highlighted with the current discussion about hepatitis B vaccine. For example, in Greece, the prevalence of anti-HBV among health workers is 40–50% and in medical and nursing students it was 12 and 17%, respectively. Screening costs around $25, whereas vaccine costs approximately $140 and so it seems reasonable to vaccinate health care workers after screening, and medical and nursing students without screening. In the UK the problem of finance is very relevant because additional funds may not be made available to health authorities and so again, screening may be resorted to as a cost saving exercise.

1.15. Targets for antiviral drugs

The development of an antiviral drug is a major undertaking and will require, at least for a private company, that the market for a drug is large enough to correspond to the cost and risk of development. Table 1.16 lists some viruses which have been ranked according to different variables in an attempt to select a good candidate for an antiviral drug. The incidence of the virus disease is naturally an important factor, as is the severity of the disease. The incidence can be obtained for diseases being reported in accordance with local regulations, but in many cases viral diseases are not reported and the incidence has to be calculated from different surveys. Also a grading of the severity is not easy and an example is when herpesvirus
infections are handled as a group, which would include both herpes encephalitis and cold sores. Therefore, a rather subjective average has been used in Table 1.16. An additional important factor in deciding the targets for antiviral chemotherapy is the absence or availability of good viral vaccines and the probability of developing vaccines in the future. For viruses like rhino and influenza with many serotypes or antigenic variants, vaccine production may always be a problem especially with influenza when new antigenic types appear rapidly. In the case of HSV-1 and HSV-2 infections the development of a successful vaccine seems unlikely when one considers that patients with frequent episodes of labial or genital herpes have high titres of neutralizing antibodies and that reinfection can occur in spite of circulating antibodies. Aspects of vaccines are discussed in more detail in Chapter 2 and in connection with the different viruses.

Rapid diagnosis (preferably by the patient!) is of importance since an antiviral drug is likely to have a narrow spectrum of activity and the virus to have a short time period of replication. It will be necessary to know exactly which virus is causing the infection and thus which drug should be used. The self-diagnosis of recurrent diseases such as labial and genital herpes is rather easy for the patient and, from that point of view, herpesvirus infections are good targets for antiviral drugs.

Major points of attack when developing new antiviral drugs are viral enzymes. Herpesvirus enzymes are easily accessible and well characterized, as are also influenza virus enzymes, and this feature also makes these two viruses attractive as targets for antiviral inhibitors. The use of viral enzymes as targets for antiviral drugs is discussed in Chapter 3. In essence, we conclude from the considerations in Table 1.16 that herpes and influenza should be major goals for the development of new antiviral drugs. This is also reflected in the literature where anti-herpes compounds are the most flourishing area at present.

### TABLE 1.16.

Rank list of candidate viruses for the development of antiviral drugs.
The listing has been made to place the virus most favourable in the development of antiviral drugs on the top of each column. The added rank numbers will then give a crude estimation of the incentive to develop an antiviral drug against each virus. The lower the number the better the target.

| Incidence | Severity | Problems with vaccine | Easy diagnosis | Accessible virus enzyme |
|-----------|----------|-----------------------|----------------|-------------------------|
| 1. Rhino  | 1. Hepatitis B | 1. Herpes             | 1. Herpes      | 1. Herpes               |
| 2. Herpes | 2. Influenza      | 2. Corona             | 2. Hepatitis B | 2. Influenza            |
| 3. Corona | 3. Herpes         | 3. Rhino              | 3. Influenza   | 3. Hepatitis B          |
| 4. Influenza | 4. Rhino       | 4. Influenza          | 4. Rhino       | 4. Rhino                |
| 5. Hepatitis B | 5. Corona | 5. Hepatitis B       | 5. Corona      | 5. Corona               |

Rank: Herpes (8), influenza (15), rhino (16), hepatitis B (16), corona (20)
TABLE 1.17.
Viruses concerned in 3 WHO Programmes

| EPI | CDD       | ARI          |
|-----|-----------|--------------|
| Measles | Rotavirus | Influenza A  |
| Poliomyelitis | Adenovirus | Influenza B  |
|       | Astrovirus | Influenza C  |
|       | Calicivirus | Parainfluenza |
|       | Coronavirus | Respiratory syncytial |
|       | Enterovirus | Adenovirus |
|       |           | Rhinovirus |
|       |           | Enterovirus |

Although not included in the six target diseases, there is a relationship between this programme and the prevention and control of diseases such as yellow fever, hepatitis, rubella and mumps.

EPI, expanded immunization programme; CDD, campaign against diarrhoeal disease; ARI, acute respiratory infections.

1.16. Outlook for the future

The great need for therapy and prophylaxis of viral diseases is obvious. In recent years we have seen a swift expansion in our knowledge of the biological and chemical processes involved in viral diseases. This has made possible rational efforts to manage and prevent viral diseases, and we are now seeing the results in new vaccines and antiviral agents.

The greatest challenges and probably the most difficult and medically important areas for prophylaxis and therapy of viral diseases are those viruses which are rapidly changing in antigenic composition and/or viruses with animal reservoirs (influenza and arboviruses) and also those forming latent infections (herpesviruses). The three major international co-ordinating programmes of WHO (Table 1.17) include both these 'challenge' viruses and also more common viruses such as measles and polio where particular help is required in developing countries. The relative role of vaccines and antiviral drugs is difficult to predict. In cases where cheap and effective vaccines exist or can be developed as exemplified for polio, measles and hepatitis B, this is likely to be the optimum control method. In cases such as influenza, the great variability of the virus probably poses insurmountable difficulties for vaccines, and makes the antiviral drug approach more promising. Finally, for viruses such as the herpesviruses, causing recurrent infections (in spite of both preexisting humoral and cell mediated immunity) vaccines seem an unlikely approach and antiviral drugs now appear to be more promising.
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