RAPID DIAGNOSIS OF VIRUS DISEASES

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Virus infections which may cause severe or life-threatening illnesses meriting chemotherapy are surveyed. Experience has shown that effective antiviral chemotherapy must be given early in the illness, and so this paper concentrates on the earliest symptoms of the various diseases and on methods leading to rapid diagnosis. This can be made by recognizing virus particles of characteristic morphology, if they occur in large numbers, e.g. rotavirus in diarrhoea. Sensitivity may be enhanced by using immune serum to trap viruses. A variety of very sensitive immunological methods is now available for detecting virus-specific proteins in secretions of the respiratory and alimentary tracts. Monoclonal antibodies help to make these more specific. Virus nucleic acids can also be detected in secretions and cells in situ by hybridization with purified radio-labelled nucleic acid. Virus diseases specifically surveyed include varicella zoster and measles, both very important in immuno-suppressed patients; epidemic influenza; and the human papilloma viruses, of which 33 different types are now known, and which cause not only common warts on hands and feet, but also variously transmitted inapparent papillomas upon the surface of the uterine cervix, often leading to cervical carcinoma. The problems of diagnosis of acquired immunodeficiency syndrome are reviewed. The aetiology of chronic non-A, non-B hepatitis is still largely obscure, but a retrovirus may be involved. The diagnosis of rabies is also considered.

This review will consider those infections from acquired immunodeficiency syndrome (AIDS) to zoster, likely to become severe enough to warrant expensive and sometimes toxic, dangerous or uncomfortable treatment, survey the earliest symptoms which might lead to a helpful diagnosis and examine the new laboratory methods for identifying the virus responsible.

The process of virus replication is sometimes confined to one or more discrete areas in the cytoplasm. These can usually then be stained and often appear as eosinophilic cytoplasmic inclusions in the light-optical microscope. Sometimes, as in rabies, their structure is quite characteristic, and finding them allows a firm diagnosis to be made. Sometimes intranuclear inclusions can be found; but one cannot tell by light microscopy whether an intranuclear inclusion is caused, for example, by a herpes virus or a papovavirus. Virus-specified proteins can be identified, whether in inclusions or diffused through the cell by serological methods. Virus nucleic acid can also now be detected in some infections. Finally, a virus infection may lead to the release of interferon (IFN) from the cell. The cellular events consequent upon virus infection can be used to detect infection by a wide variety of viruses and will be referred to further under the headings of the different virus diseases.

Methods Leading to Rapid Diagnosis

Few parts of the body are now out of reach of the tip of an enquiring tube or needle. For instance, the whole alimentary tract is now accessible. Secretions can be taken from the nasopharynx or by bronchoscope. Brain biopsy has been used to diagnose herpes encephalitis by immunofluorescent staining. Of course, the skin is easily accessible and even cardiac muscle biopsy is now possible. Some viruses and methods are listed in Table 1.

Virus Recognition

Where virus particles of characteristic morphology are present in large numbers, they can at once be recognized by examination of the specimen negatively stained in the electron microscope. For a moderately-sized virus, e.g. rotavirus, the detection limit is about 10^6 virus particles per gram of material, although detection is much easier if there are 10^6 particles. Viruses are normally present in very large numbers in the skin lesions of herpes/varicella zoster. Hepatitis virus particles can be detected in the sera of hepatitis carriers or of patients with acute hepatitis. The recently identified parvovirus can be detected in blood by electron microscopy in the early stages of infection. Viruses having no very characteristic appearance can be identified by immune electron microscopy by mixing the patient's specimen with a specific antiserum and

![Table](image)

| Virus group or other | Electron microscopy (negative staining) | Enzyme-linked immunoassay | Reverse passive Haemagglutination | Immuno fluorescence | Radio immunoassay |
|---------------------|----------------------------------------|---------------------------|---------------------------------|-------------------|-----------------|
| Varicella zoster     | Herpes group, including varicella zoster | Hepatitis B Rotaviruses   | Influenza A and B Respiratory    | Hepatitis A and B | Para-Influenza 1-4 Rotaviruses |
| Molluscum contagiosum | Cytomegalovirus (especially for antibody) | Rotaviruses | Respiratory |  | Para-Influenza 1-4 |
| Rotaviruses          | Adenoviruses |  | | Adenoviruses |  |
| Adenoviruses and other | Adenoviruses |  | | Rotaviruses |  |
| "small round viruses" | Hepatitis A and B |  | |  | |
| Caliciviruses        |  |  | |  | |
| Coronavirus-like particles |  |  | |  | |
| Parvoviruses         |  |  | |  | |
| Varicella           |  |  | |  | |

Virus infections for which nucleic acid hybridization methods, e.g. 'dot-blot' have been used. Papova group, herpes group, especially cytomegaloviruses, hepatitis B and rotavirus. Other applications, e.g. for adenoviruses and retroviruses are likely to follow soon.

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allowing it to react — 1–3 h is usually sufficient — and then centrifuging and examining the deposit, negatively stained, in the electron microscope. Sensitivity can be greatly increased by coating with antibody the carbon membrane on the grid. The grid is then washed and negatively stained. This 'fly-paper' method increases the sensitivity of particles detected by up to 1000-fold. It works very well for plant viruses (for which it was first developed) and usually works well for enteric viruses in human faeces; but for other mammalian material it has not worked so well, perhaps because mammals make antibodies early in the course of infection and these antibodies adhere to the virus particles and block their adhesion to specific antibody upon the grid. When virus has been trapped, it can be identified by labelling with specific antibody.

**Immunological and Chemical Methods for Virus Detection**

One can detect virus-specific proteins in nasopharyngeal aspirates of children with acute respiratory tract infections. The cells from these can be centrifuged on to glass slides and are then fixed. The fixed slides can be sent through the post to the laboratory. This method is about as sensitive as virus isolation and a same-day diagnosis can be provided for the clinician.1

Radioimmunoassays and immunoenzymatic assays have been devised also to detect a variety of virus IgM antibodies, including those of rubella, measles, mumps, tickborne encephalitis, adenovirus and rotavirus.2 Monoclonal antibodies help very much in developing a really specific reaction.

Hepatitis A and B can be diagnosed by detecting the antigen in faeces and blood respectively by radioimmunoassay.3 This method is very sensitive, detecting quantities of antigen in pg/ml rather than ng/ml concentrations. The method is to attach a 'capture antibody' to the solid phase, which may be a polystyrene bead, or the bottom of the well in a polystyrene microtitre plate. To this is added a suspension of virus. The virus, if present, adheres to the antibody. A second antibody — often nowadays a monoclonal antibody — is added. If virus has adhered, so will the monoclonal antibody. Anti-mouse IgG antibody which has been labelled either with enzyme or with radioactive iodine is then added and the reaction is read, either by developing colour in a chromogenic substrate for the enzyme, or by counting radioactivity in a counter.

Until recently, radioimmunoassay was by far the most sensitive method of detecting virus antigen, but two improvements in the enzyme-linked immunosorbent assay (ELISA) method have come along fairly recently, and offer considerably increased sensitivity. The first relies upon coupling antibody with galactosidase and the use of umbelliferyl β-galactoside as substrate. The product of the enzyme activity fluoresces in ultraviolet light. Fluorescence can be read by the dark-adapted eye without the use of a spectrophotometer. Sensitivity has recently been increased further by using a peroxidase label. In the presence of hydrogen peroxide, this catalyses the oxidation of luminol or isoluminol and light is emitted. The light emission is enormously enhanced by synthetic firefly θ-luciferin, and is thus readily detectable; it decays comparatively slowly over several minutes. All one needs is a good luminoimeter to quantify the light. Other hydroxybenzothiazoles can also be used to enhance light emission by up to 1000-fold.4–6

This, and time-elapsed fluoroimmunoassay, are likely to greatly enhance the sensitivity of detection of virus antigens in material taken directly from patients.

The ELISA system has also been improved by better coupling of enzyme with antibody using a biotin–avidin linkage, which allows the attachment of more enzyme molecules to an antibody molecule than do the conventional methods.6b ELISA tests have the disadvantage in hot countries that enzyme conjugates, even when freeze-dried, may lose activity in transit.

One can also detect virus antigens by reverse passive haemagglutination. Here, virus-specific antibodies are attached to erythrocytes and, when these are mixed with a suspension of clinical material containing viruses, e.g. hepatitis serum, or supernatants of faeces containing rotaviruses, the virus acts as a 'glue', sticking the antibodies on one erythrocyte to antibodies on another, and so causing agglutination. Freeze-dried antibody-coated cells are more stable than most antibody-enzyme conjugates. Reverse passive haemagglutination works particularly well with some monoclonal antibodies.

A new type of immunoassay called time-resolved fluoroimmunoassay7 has recently been developed, mainly in Scandinavia, by the LKB factory in collaboration with Professor Halonen in Finland, and has been used for virus diagnosis.8 The basic principle is that, instead of an enzyme, a rare earth element, europium, is attached to antibody. A 'capture' antibody method is used. Virus protein, if present, is trapped by the capture antibody. The virus antigen is then reacted with a second antibody. This, in turn, is reacted with a europium-labelled antioglobin antibody. After treatment with a fluorescence enhancing solution, the europium is made to emit light, by stimulating it with a very intense xenon flash, or laser pulse.

Virus DNA can be extracted from viruses such as cytomegalovirus (CMV), papilloma etc., and cloned into a bacterial plasmid. The bacteria containing the plasmid can be grown up in great quantity in a medium containing a radioactive label. The radioactive plasmids can then be extracted, the virus DNA fragment cut out of the plasmids with the aid of restriction enzymes and used as a 'probe'. Other methods of making DNA probes are also available. One does not have to use the whole of the nucleic acid; a short nucleotide sequence may be sufficient. This method can also be used for an RNA virus; its RNA can be transcribed to DNA using reverse transcriptase enzyme, and the complementary DNA (cDNA) thus obtained is cloned into a bacterium. The DNA will hybridize with virus RNA in a 'dot-blot' test. This has been used to detect rotavirus double-stranded (ds) RNA in faeces4 and the sensitivity compares well with that of the ELISA test. For such tests, virus-containing material is broken up to liberate the nucleic acid, usually by treating it with sodium hydroxide. The nucleic acid can then be blotted to give a spot on a nitrocellulose membrane; the labelled DNA probe is then applied. If virus nucleic acid is present in the membrane, the labelled probe attaches to it. The result can be recorded by an autoradiograph. The probe need not be radioactively labelled; it can be labelled using a biotin–avidin link with an enzyme or fluorescein leading to fluorescence or a coloured enzyme product. The method can be used to detect virus nucleic acid in cells that are not making complete virus, as for example to detect Epstein–Barr (EB) virus DNA sequences in Burkitt lymphoma cells or hepatitis B sequences in hepatocytes. As few as two virus DNA copies per cell can be detected. The basic principles have been well described by Steele.9,10

Application of these various methods will be mentioned under the different virus infections described below.

### Some Virus Diseases

**Varicella**

Almost always, in previously healthy people, varicella is a comparatively mild disease with an incubation period of about 12–14 days and sometimes a prodromal fever of 1–2 days.
Occasionally, especially in adults, a severe disease may result with a confluent or semi-confluent rash and a sustained high fever. Rarely, there may be a genuine varicella pneumonia, which is indicated by shortness of breath and cough, sometimes with haemoptysis. X-ray examination reveals diffuse patchy opacity.

In the immunosuppressed, the rash tends to be much worse, and is frequently haemorrhagic, particularly in patients being treated for leukaemia or lymphoma. Pneumonia is comparatively common. The rash can be quite atypical; antimitobolites prevent the development of the erythematous margin around the varicella vesicles. Low-power microscopy of vesicle fluid reveals large cells with the hypertrophic nuclear structures or inclusion bodies characteristic of herpes type infections. The diagnosis is then usually confirmed by electron microscopic examination of vesicle fluid. The difficulty with pneumonia associated with varicella is to determine whether the pneumonia is caused by the varicella or by some intercurrent agent. Tracheal aspirates or, better, examination of fluid obtained by lung puncture using many of the newer, very sensitive and specific tests for virus and other pathogens may serve to establish the diagnosis. If effective chemotherapy is to be given, a precise diagnosis is essential.

Zoster

The reactivation of varicella virus which has become latent in the dorsal root ganglia takes place when the patient's immunity falls years after the initial infection, or when the host's immunity is deliberately suppressed. In immunosuppressed subjects, infection may become widespread and serious, with haemorrhagic lesions, and may extend to the central nervous system, causing meningitis or meningoencephalitis.

Laboratory diagnosis is usually unnecessary; the clinical features are obvious enough. Pain over a nerve followed by the eruption of vesicles along it is diagnostic; so is the combination of pain with analgesia over a nerve segment. In the very ill or immunosuppressed, the lesions may be haemorrhagic or otherwise atypical. Diagnosis can be established rapidly by finding characteristic virus particles by electron microscopy in skin lesions and/or in cerebrospinal fluid (CSF) and/or by detecting virus antigen by immunofluorescence or ELISA.

Cytomegalovirus

About half the population are infected by CMV in the first five years or so of life. Another quarter are infected in their teenage years. (These proportions vary in different communities.) The infection is usually subclinical, but sometimes there may be a mild rash or a glandular-fever-like syndrome.

Infection is important if it occurs for the first time in pregnant women, when the virus may be transmitted across the placenta to the infant in whom it may cause a range of diseases from the inapparent to a mild illness, sometimes with a slight rash, in which the child becomes ‘twitchy’ indicating central nervous system (CNS) involvement, to the full-blown syndrome of microcephaly with cerebral calcification and disseminated infection with multiple cytomegalic cells in all the organs of the body. Congenitally infected children excrete virus in considerable quantity in the urine. The so-far insuperable problems of prevention and treatment of CMV infection of fetus and infant have recently been well reviewed.

Diagnosis can rarely be made by finding inclusion-bearing cells in the urine, but much more easily by isolating the virus in tissue culture, although two or three weeks often elapse before a cytopathic effect appears. More rapid diagnosis may be made by staining inoculated tissue cultures for immunofluorescence one or two days after inoculation. Once a person is infected, the virus genome becomes incorporated into the cell genome, especially in the lymphocytes and probably elsewhere, and persists for life. This carrier state is indicated by finding antibody in the blood. An ELISA test is usually used to screen blood for exchange transfusion to infants and for transfusion into antibody-negative persons being immunosuppressed for kidney or bone marrow transplantation.

Primary infection in the immunosuppressed leads to widespread multiplication of the virus in the body and may cause serious illness in those receiving kidney transplants, though this is less of a problem nowadays than in earlier years when higher doses of immunosuppressants were employed.

For children receiving bone marrow transplantation, however, the infection is often severe with pneumonia and even encephalitis, and may be lethal. In those previously infected, immunosuppression may cause reactivation and extensive virus replication in many organs. Immunosuppression suppresses symptoms too, and usually the only clinical indication of infection is unexplained fever. Although much virus is shed in the urine, an IgM antibody response may not develop. Tissue culture is too slow to give a really rapid diagnosis; and ELISA fails to detect CMV in urine, so a ‘dot-blot’ detection of the CMV genome in the urine has been developed using radiolabelled CMV DNA probes. This test is now available commercially and gives an answer within 24 h.

Epidemic Influenza

The incubation period is ordinarily 1–2 days. The patient suddenly feels chilly, with headache and malaise and aching of the muscles of the limbs and back, followed frequently by a dry cough often with substernal pain. Occasionally, symptoms are preceded by nasal symptoms and the illness may resemble a ‘heavy cold’.

The range of severity varies from subclinical reactions to a fulminating influenza causing death in a few hours, with a haemorrhagic broncho-alveolar pneumonia. In about 10% of those infected, the disease may begin with vomiting. The average patient’s temperature rises rapidly to 38–40°C within 24 h and then, oscillating somewhat, declines to normal by the 3rd–5th day. A sudden deterioration with a rise of pulse rate and fever indicates that secondary bacterial pneumonia may be setting in and urgent antibiotic treatment is necessary. In those with pre-existing pulmonary or cardiac disease, influenza may be very much more severe and sometimes fatal; usually death is caused by a secondary bacterial infection, but in cardiac or respiratory cripples, fatal cases of influenza without secondary bacterial infection do occur.

In the most severe cases which may suddenly follow what appears to have been a mild disease for one or two days, acute dyspnoea and prostration develop; within a very few hours the patient is dangerously ill, presenting as shocked with tachycardia, pale grey or cyanosed, with a weak pulse and low blood pressure; temperature may be normal, and a thin frothy exudate is seen from the respiratory tract.

In about 25% of children up to age 10, influenza may present as croup. In older children, croup is less common and the diagnosis is more easily made: cough is common, the throat may be sore, muscular aching is sometimes severe and fever and headache are prominent.

In clinical diagnosis it is very difficult to distinguish an early case
of influenza from other varieties of respiratory tract infection, certainly in the early stages, especially when the influenza is not widely prevalent. Infection may rapidly be demonstrated by immunofluorescence or radioimmunoassay in sputum or nasopharyngeal aspirates, especially in children.\textsuperscript{26}

Other Respiratory Virus Infections

Respiratory syncytial virus (RSV) causes a very characteristic syndrome in young children. After an incubation period of about five days, an upper respiratory tract infection begins with snuffles and nasal discharge. Then, in very young children — those under six months are the most severely affected — lower respiratory changes begin. There is a moderate fever, usually with a rapid pulse. The child has difficulty, just as in allergic asthma, in completing expiration. Breathing difficulties cause the child to be admitted to hospital. Mortality is about 2%, higher in children of the poor. The virus infects and causes obstruction of the terminal bronchioles, which in the very young child are very narrow. Breathing usually eases after two or three days and the child can then be sent home. Rapid diagnosis can easily be made by radioimmunoassay (RIA) or immunofluorescent staining of nasopharyngeal aspirates.\textsuperscript{1,27}

Pneumonia in infants and young children may be due to infection with RSV, para-influenza types 1-3, influenza virus and occasionally adenoviruses. These can be diagnosed by immunofluorescence on aspirated nasopharyngeal secretions.

Apart from epidemic influenza, there exists a wide variety of upper and lower respiratory tract infections caused by numerous different viruses which are prevalent especially during the winter. The more severe illnesses, especially in adults may be labelled 'flu'. Viruses responsible are rhinoviruses and respiratory coronaviruses, which usually cause common colds, sometimes with sore throat, and occasionally venture downwards to cause bronchitis. Clinically, nasal obstruction, profuse nasal discharge and absence of fever and myalgia indicate a cold rather than influenza. The distinction is easy enough when dealing with a group of people, but may be impossible in an individual patient.

Several serotypes of adenoviruses, especially types 3 and 7, cause the syndrome of adenopharyngoconjunctival fever characterized by pharyngitis, fever and conjunctivitis. The virus is easily isolated in most human tissue culture cell lines. Adenovirus type 4 can cause influenza-like outbreaks, especially among military recruits, both in the USA and the UK. Sporadic cases of infection in the general population from adenovirus 4 are rare or, at any rate, rarely diagnosed. The incubation period is about a week. Some serotypes of adenovirus, usually type 8 and occasionally 19 but rarely others, cause acute epidemic keratoconjunctivitis (EKC), especially in shipyards and in hospitals. Virus is transferred by direct contact from person to person, or (in eye hospitals) by immunofluorescence on aspirated nasal secretions. Apart from epidemic influenza, there exists a wide variety of upper and lower respiratory tract infections caused by numerous different viruses which are prevalent especially during the winter. The more severe illnesses, especially in adults may be labelled 'flu'. Viruses responsible are rhinoviruses and respiratory coronaviruses, which usually cause common colds, sometimes with sore throat, and occasionally venture downwards to cause bronchitis. Clinically, nasal obstruction, profuse nasal discharge and absence of fever and myalgia indicate a cold rather than influenza. The distinction is easy enough when dealing with a group of people, but may be impossible in an individual patient.

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**Herpes Simplex Viruses**

Herpes simplex viruses (HSV) are divided into two types: HSV 1 and HSV 2. Type 1 infects mostly the face and mouth, sometimes also causes lesions upon the hand (whitlow) and is the type usually found in acute encephalitis. Type 2 is usually associated with urogenital infections, but type 2 infections may be found in and around the mouth and type 1 infections in and around the external genitals.

Acute primary herpes simplex in young children can, however, be a serious and severe illness with florid, multiple ulcers and vesicles in and around the mouth, cervical lymphadenitis and a high fever. In children with eczema or in those with extensive burns, a primary herpetiform infection can become very severe and may be life-threatening. Infection may be severe in the immunosuppressed.\textsuperscript{29}

Herpes simplex keratitis can usually be recognized clinically and confirmed by virological tests. Stromal keratitis results from invasion of the deeper layers of the cornea with the herpes virus; much of the damage is caused by a hypersensitivity reaction.\textsuperscript{30}

HSV encephalitis is fortunately rare; about one severe case per million of population per year.\textsuperscript{31} The disease is commoner in children than in adults and seems always to be caused by HSV 1. The patient first presents with headache and fever and early malaise. Some patients show early personality changes and about half have fits early in the disease. Headache and fever become worse and the patient goes into coma within a very few days. Localizing signs are often present and indicate a lesion in the temporal lobe on one or other side and most of the signs and symptoms are otherwise caused by cerebral oedema which may be reflected in oedema and swelling of the optic disc. Without treatment, the infection is usually fatal. The differential diagnosis in a child is likely to be a cerebral vein thrombosis, early meningitis or an abscess. In the early stages of the disease, more than 50 cells cm\(^{-3}\) in the CSF usually points to some other diagnosis; a low sugar level is also likely to indicate a bacterial infection. Workers in the UK and USA used to make a brain biopsy of the temporal lobe to establish a diagnosis beyond doubt before starting treatment. This procedure of itself does not carry a very high risk, but experience has shown that, if treatment is delayed until one is suspicious enough to make a brain biopsy, one has probably waited too long.\textsuperscript{31} It is better to attempt to make a retrospective diagnosis by looking for IgM antibodies appearing in the CSF. These antibodies do not appear early but, as the more modern antiviral agents, especially acyclovir, are comparatively non-toxic, one can afford to 'shoot first and ask questions later'. Inevitably, some patients who do not have herpes encephalitis will thus be treated, and they probably will be none the worse for that. It is important, however, to make certain in patients whose symptoms progress that one is not missing tuberculous meningitis or brain abscess or other treatable cause of symptoms. A computerized axial tomography (CAT) scan or, better still, nuclear magnetic resonance (NMR) scan of the brain helps to establish the diagnosis, but one must repeat that the best results are likely to be obtained in people treated at such an early stage that radiologically detectable lesions are not yet present.

**Human Papilloma Viruses**

When a clarified suspension of ground-up warts is examined in the electron microscope, one can often find numerous virus particles. However, since 1976, biochemical and serological investigation of human papillomaviruses has revealed that there are many kinds, all similar in structure, but different in nucleotide and antigenic composition. Different human papillomaviruses may be particularly associated with different types of warts. The earlier work, up to 1980, was well reviewed by Coleman.\textsuperscript{32}

Several different warty syndromes can be recognized. The ordinary warts on the hands and feet of children and adults virtually never undergo malignant transformation and are transmitted by direct or indirect contact through minor abrasions. Virus
particles in warts are frequently found in extremely large numbers, but mostly in common plantar and palmar warts. In genital warts, virus particles are very much less numerous. Genital warts in both men and women sometimes progress rapidly to very large fungating confluent and infiltrating masses. They are transmitted by sexual contact. Small cervical warts are comparatively common and are frequently found in combination with herpes type 2 infections. Virus diagnosis can be made by nucleic acid ‘dot-blot’ hybridization. It may well be that papilloma and herpes viruses act synergistically in the causation of cervical carcinoma; the lesions do sometimes proceed to malignancy. Immunosuppression is a risk factor. Infection may be passed on to infants passing through the warty birth canal; these infants may subsequently develop laryngeal papillomas. These may have to be treated surgically to allow an adequate airway, but do not usually go on to malignant change, and eventually disappear spontaneously. A rare warty skin disease is epidermodysplasia verruciformis. In this, the patient becomes covered all over with warts, usually flat warts, which develop in early infancy and persist throughout life. The lesions transform into epidermal carcinoma in about a quarter of these patients even in their 20s and 30s. Papilloma virus particles can be found in the benign lesions, but not in malignant tumours derived from them.

Human papilloma viruses have been differentiated by extracting their virus-specific DNA, and examining the pattern given by electrophoresis of the DNA fragments after cleavage by restriction enzymes. About 33 different varieties have been recorded. Most of these are associated with epidermodysplasia verruciformis. Two or more different DNA varieties have been reported from the same tumour. The clinical diagnosis is apparent enough, and it is likely that the same antiviral compounds will be effective against all of these viruses.

**Acquired Immunodeficiency Syndrome**

This disease was first recognized in early 1981 and some cases occurring in 1979 were diagnosed retrospectively. It is due to a blood-borne infection most frequently transmitted by sexual contact, especially between male homosexuals, by transfusion and by Factor VIII. The origin of the virus (human T lymphocyte virus III — HTLV* ) is obscure; one suggestion is that it was originally introduced from Central Africa. Transmission from mother to baby has been reported.

The syndrome is an underlying cellular immunodeficiency complicated by an opportunistic infection, often pneumocystis pneumonia, or associated with Kaposi's sarcoma in someone under 60 years old. Progressive multifocal leuкоencephalopathy has been found in some victims and HTLV III itself may cause CNS lesions.

The disease may be preceded by the extended lymphadenopathy syndrome, defined as unexplained lymphadenopathy in two or more extra-inquinal sites persisting for at least two or three months, and associated usually with fever, malaise, night sweats, weight loss and hepatosplenomegaly. The presence of infection may be indicated by finding IFN-α in the circulation, but the causative virus can be isolated from lymphocytes and tests for antibody are generally available.

It may yet be possible to detect virus by rapid tests such as competitive radioimmunoassay for immunofluorescence or with DNA probes for HTLV III or related viruses.

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* HTLV III is also known as lymphadenopathy-associated virus.
Korean haemorrhagic fever (Hantaan virus) is an infection carried by voles which excrete virus in their urine. There appear to be severe and mild varieties. Hantaan virus is widespread over a large part of the northern hemisphere. The symptoms consist of fever, a haemorrhagic rash on the skin, especially upon the chest, raised transaminases and marked renal signs, especially raised blood urea, albuminuria and passage of erythrocytes. Differential diagnosis in the UK is from Weil's disease (caused by Leptospira icterohaemorrhagiae). Rapid diagnostic tests for Hantaan infection are still being developed but diagnosis can be made by finding antibody in the patient's serum a few days after onset.

Treatment of persons with clinical signs of rabies has so far been extremely disappointing.61 If any success is ever to be obtained, it is likely that treatment will have to begin at a very early stage of the clinical syndrome. Rabies may be suspected in anyone returning to the UK from abroad with a history of an untreated bite. Early symptoms are anxiety, agitation, depression or psychotonic symptoms. Nausea, vomiting, malaise, lethargy and paraesthesia at the site of the bite are also indications. Diagnosis may be made by virus isolation or more rapidly by biopsy of the skin at the edge of the scalp or by corneal scrapings, and then staining the tissue for immunofluorescence using specific antirabies serum. Virus antigen may be detected in saliva by the newer, extremely sensitive, serological tests. Treatment has to be commenced on clinical suspicion. As the disease evolves, the appearance of aphasia and incoordination, paresis and paralysis and particularly hydrophobia with laryngeal spasms when attempting to drink, may make the clinical diagnosis easy but by this stage prospects for successful treatment are bad.61

Acute Infectious Diarrhoea

Viruses, especially rotaviruses, and to a lesser extent adenoviruses, are the commonest infective agents. All age groups are affected but virus diarrhoea is important in young children up to the age of five years and in the aged.62 In developed countries, the disease is usually mild and, with expert paediatric care, fatalities are extremely rare. In tropical countries where malnutrition is rife, distances to hospital are great and transport slow, deaths are numerous, mainly from dehydration. The viruses cause diarrhoea by infecting the enterocytes on the tips and sides of the villi of the small intestine. Animal experiments indicate that such virus replication has usually occurred by the time serious diarrhoea has set in. The damaged cells are replaced within 5-8 days by new cells growing up from the crypts of Lieberkuhn; these new cells are incompletely differentiated and are not attacked by rotaviruses, and so the disease is normally self-limiting.63

In children suffering from ‘combined immunodeficiency syndrome’, however, rotavirus diarrhoea and virus excretion may persist for months, and is very difficult to treat.64

The best available treatment is to give the child oral rehydration solution by mouth in good time — either the WHO formula, or, as favoured by paediatricians in temperate countries, a solution containing a little less sodium; but both work well. Hopes of an effective rotavirus vaccine are rising. So far, there is no effective antiviral compound for rotavirus infection.

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