the body's defences against invasion by potential pathogens or as a side-effect of drugs and other therapeutic measures. Their particular frequency as iatrogenous diseases has made them a danger common enough and grave enough to necessitate constant watch for their development when any patient is under treatment with corticosteroids, cytotoxic agents and broad-spectrum antibiotics, or with radiotherapy.

'Opportunistic infections' are often the immediate cause of death in cases of chronic debilitating disease, particularly cancer. In assessing their importance in cases of this sort it has to be remembered that they have to some extent taken the place of terminal bronchopneumonia as the closing stage in the course of the illness. Many patients with cancer nowadays live much longer than would have been the case before the introduction of modern advances in the treatment of neoplastic diseases; moreover, simple pneumonia in these patients is often not the danger that it was once, for it may be cut short and cured by giving antibiotics. Many of the micro-organisms that cause 'opportunistic infections' are resistant to drugs, or respond only to treatment with drugs, such as the antifungal antibiotic, amphotericin B, of which the side-effects are liable to be particularly dangerous in these chronically debilitated patients. It is sometimes the case, then, that there is nothing to be done to overcome an 'opportunistic infection'. As has been mentioned, this cannot be an excuse for failure to establish early diagnosis of the presence of such infections – their prevention, or their successful treatment, may provide the chance of bringing the patient's underlying disease under control and, at least in some cases, of restoring his health.

The four cases summarized in this paper include instances of infection by bacterial, fungal, viral and protozoal 'opportunists'. In one of the cases all four of these groups of organisms were represented, and no fewer than seven different types of organism were recognized at necropsy.

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Human Cytomegalovirus Infection

The cytomegaloviruses are members of the herpesvirus group which is responsible for probably the majority of opportunistic viral infections. They are the prime examples of the group in this respect, since they have been recognized to cause disease almost exclusively in individuals with impaired immunity responses. However, there is increasing evidence that the clinical spectrum of cytomegalovirus infection is wider than previously believed.

Until a few years ago the diagnosis of cytomegalic inclusion disease was possible only by histological methods and was usually made unexpectedly at post-mortem. The histology is characterized by the presence of cytomegalic cells. These are very large cells with a large nucleus containing a prominent inclusion body. In stained tissue sections the inclusion body is typically surrounded by an unstained halo giving rise to the so-called 'owl's-eye' appearance. The recognition of cytomegalic cells in the urine provides a method, an insensitive one however, of diagnosis during life (Fetterman 1952). Nor is histological examination of tissues obtained by biopsy or at post-mortem always reliable for diagnosis, as cytomegalic cells can be scanty or absent even when virus is readily isolated from the same specimens (Hanshaw & Weller 1961, Weller & Hanshaw 1962, Stern *et al.* 1963). In the body the virus is predominantly epitheliotropic, although mesothelial cells are occasionally affected especially in adults. This is in striking contrast with the situation in tissue culture where the virus has been grown only in fibroblasts; the cytopathic effect is similar to that in the body with the formation of cytomegalic cells having large intranuclear inclusion bodies. Electron microscopy confirms that the virus belongs to the herpesvirus group by showing that the structure of its capsid is identical with that of herpes simplex virus (Smith & Rasmussen 1963, Wright *et al.* 1964). The capsid develops in the nucleus of the infected cell and subsequently collects an outer envelope from the surface membranes of the cell (Stern & Friedmann 1960).

On the basis of post-mortem studies two forms of cytomegalic inclusion disease have been recognized, disseminated and localized. The severest and most characteristic example of disseminated disease occurs in the newborn. These cases acquire their infections *in utero* and the clinical features, which are present at birth or appear shortly afterwards, include jaundice with hepato-

splenomegaly, thrombocytopenic purpura, erythroblastic anæmia, pneumonitis and often evidence of neural damage which may be associated with periventricular cerebral calcification. They often die but recovery does occur although it may be followed by residual abnormalities of which the most frequent is microcephalic mental deficiency (Weller & Hanshaw 1962, Medearis 1964). In older infants disseminated disease is almost always superimposed on other serious debilitating diseases, so that its clinical pattern is less well defined but usually takes the form of an unresolving pneumonia or sometimes intractable gastrointestinal symptoms, often with evidence of hepatic and renal dysfunction (Smith & Vellios 1950, Wyatt *et al.* 1950, Medearis 1957). The true incidence of the neonatal and postnatal diseases is uncertain since many of the fatal cases and of those that recover are undiagnosed. They have accounted for as many as 1–2% of unselected pædiatric autopsies in the United States as well as in Germany and Finland, but in this country they have rarely been reported (Farber & Wolbach 1932, McCordock & Smith 1934, Wyatt *et al.* 1950, Ahvenainen 1952, Seifert & Oehme 1957). After 4 years of age the disease appears to be extremely rare. All the reported cases, both in children and adults, have been recognized unexpectedly at post-mortem or in biopsy specimens taken for other purposes (Wong & Warner 1962). They have occurred almost invariably as a complication of underlying chronic debilitating conditions such as leukæmia and lymphoma which depress the normal defence mechanisms of the body, especially when steroids and cytotoxic drugs have been used in treatment.

The localized form of the disease, on the other hand, is much more common. It occurs as an inapparent or symptomless infection in early childhood, and is recognized by the presence of typical cytomegalic cells in the salivary glands and occasionally in the kidneys. Such cells are an incidental finding at post-mortems on children who have died from other causes. They have been described in 10–12% of unselected post-mortems carried out on children in the United States and Germany (Farber & Wolbach 1932, McCordock & Smith 1934, Seifert & Oehme 1957), and in 18% and 32% of autopsies in Venezuela and Indonesia respectively (Potenza 1954, Prawirohardjo 1938). In Great Britain the incidence is 5% or less (Baar 1955, McDonald, personal communication).

Localized disease is very rare in adults. When it occurs the cytomegalic cells are found not in the salivary glands but in the lungs in association with various types of pneumonia or in the gastrointestinal tract around granulomatous lesions.

Serological Study of Infection in London

Post-mortem studies suggest that cytomegalovirus infection occurs predominantly in young children, mostly as a subclinical infection with the formation of cytomegalic cells locally at the site of entry and primary multiplication of the virus, namely in the salivary glands. Disseminated disease follows apparently only when circumstances are opportune. These are other diseases and treatments with steroids and cytotoxic drugs which depress the immunity mechanisms of the body, and also the fœtal and newborn states in which the immunity mechanisms are immature. However, serological investigations, using tissue culture antigens which became available after the isolation of the human cytomegalovirus in tissue culture in 1956, demonstrated that infection was very much more widespread than previously suspected, both in children and adults (Smith 1956, Rowe *et al.* 1956, Weller *et al.* 1957).

Such a serological study in the London area (Stern & Elek 1965) has shown that infection in early childhood is infrequent, with only 4% of children under 5 years of age possessing complement-fixing antibodies. This corresponds closely with results obtained from post-mortem examinations of salivary glands of small children in this country. In other countries the incidence of antibodies in young children is often much higher (Rowe *et al.* 1956, Rowe 1960, Mendez-Cashion *et al.* 1963) and this is undoubtedly related to standards of hygiene. As with polioviruses improved hygiene reduces the chances of infection in early childhood and the first large increase in infection occurs among children at school. In London the incidence of antibodies increases with age in schoolchildren to 15% at 10 years and 22% at 15 years. Maximum incidence is not reached until 25–35 years of age when 54% of the adult population have antibodies. In view of the fact that almost a third of women are infected and acquire their antibodies between 15 and 35 years of age, the main child-bearing period, it is surprising that neonatal disease is apparently so rare in this country as compared with others. Almost certainly it is more common than generally recognized. Not only are typical cases misdiagnosed, but the disease also occurs in a milder form without the full classical clinical picture. One such case was a newborn baby who was apparently healthy but had an enlarged liver (Stern & Tucker, unpublished). She was found to be excreting cytomegalovirus in the throat and urine. Six months later she was still thriving but with persistent hepatosplenomegaly and continuing virus excretion. The incidence of complement-fixing antibodies in the London population over 35 years of age is maintained at over 50%. This suggests, by analogy with herpes

simplex, that primary infection is followed by persistent latent infection. Activation of such latent infection occurring as a complication of diseases and treatments which depress the defence mechanisms of the body has been invoked to explain the rare disseminated disease in older children and adults (Nelson & Wyatt 1959), although it is possible that some of the cases follow exogenous infection and that dissemination is the result of immunity failure. The increasing use of steroids and cytotoxic drugs should provide more opportunities for the study and elucidation of this problem by serological methods. It is not known whether otherwise healthy persons suffer recurrent reactivations as in the case of herpes simplex.

Primary infection, whether subclinical or causing severe disease, is characterized by excretion of the virus in the throat and urine for long periods, for many months or even years despite high levels of serum antibody (Rowe *et al.* 1958, Weller & Hanshaw 1962). These long-term excretors are the source of infection in the community. Infection is probably not highly contagious, requiring close contact as within family units and closed populations. The markedly higher level of infection among 10–15-year-old boys in a boarding school in London (80%) as compared with two day schools (18% and 29%) illustrates the importance of close prolonged contact for spread.

Liver Disease

Although the great majority of primary infections are subclinical, there is increasing evidence that infection can cause liver damage. This is, of course, a prominent feature of the neonatal disease, and Weller & Hanshaw (1962) have demonstrated that cytomegaloviruses are an important cause of the syndrome of 'neonatal hepatitis'. Milder forms of hepatitis without jaundice or obvious illness have also been recognized in the newborn, as in the case described above, as well as in older children. Thus Rowe *et al.* (1958) and Hanshaw & Simon (1962) found that a high proportion of small children who were excreting cytomegalovirus had abnormal liver function tests with or without hepatomegaly. I have seen 2 similar cases recently. The first was an apparently healthy 2-year-old child who was found, on routine examination, to be excreting cytomegalovirus and was then shown to have grossly abnormal liver function tests. One month later these were normal despite continued viruria. The second case was a 4-year-old boy who was seen by his doctor because of a mild respiratory illness and was discovered to have a markedly enlarged liver. Cytomegalovirus was isolated from the throat and urine. Six months afterwards he is still apparently well but with persistent liver enlargement and virus excretion. Whether the liver involvement in these cases is always transient or sometimes progresses to chronic liver disease is as yet unknown.

Mental Deficiency

Neonatal cytomegalic inclusion disease often causes severe brain damage resulting in mental deficiency and microcephaly (Weller & Hanshaw 1962, Medearis 1964). True developmental defects of the central nervous system have also been described following infection of the fœtus early in gestation, and the cytomegalovirus must now be grouped with the rubella virus and toxoplasma as known teratogenic agents (Crome 1961). As part of a larger study of mental deficiency (Stern & Elek, unpublished), 66 severely mentally deficient children aged 1–6 years were examined for cytomegalovirus antibodies. Their names were picked at random from the files of the Middlesex County Council Mental Health Department, the only proviso being that they were not mongols. The children were all living at home with their families so that the problems of cross-infection inherent in a study of institutional populations were avoided. They were compared with 115 normal children of the same age group. Nine of the 66 mentally deficient children possessed antibodies (13·6%), as compared with 5 of the 115 normal children (4·3%). This difference is statistically significant ($0{\cdot}05 > P > 0{\cdot}02$). When the mentally deficient children were analysed according to associated clinical abnormalities, namely cerebral palsy, epilepsy, microcephaly and hydrocephalus, it was found that the excess of antibody reactors could be accounted for almost entirely by the microcephalics. The correlation of cytomegalovirus infection with microcephaly was highly significant ($0{\cdot}01 > P > 0{\cdot}005$). This, therefore, confirms the findings of Weller & Hanshaw (1962) that cytomegaloviruses are an important cause of microcephalic mental deficiency, although the full extent of their role in the ætiology of mental disease requires further study.

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Pneumocystis Infection

Pneumocystis pneumonia, although a rare disease in this country, has become a serious and widespread infection among young infants in many Central European countries during the past forty years. Although the majority have been sporadic cases, several small epidemics have occurred among infants in nurseries and hospitals in some of which temporary closure of the institution has been necessary.

The clinical course and pathology of the disease had been recognized for many years but the ætiology remained unsolved until van der Meer & Brug (1942) were able to demonstrate *Pneumocystis carinii* in impression smears taken from human lungs. Later Vanek (1951) in Czechoslovakia demonstrated the causative parasite in the intra-alveolar exudate in lung sections shortly after the introduction of the PAS staining method.

The causative organism *Pneumocystis carinii* was originally discovered by Chagas (1909) in the lung of a rat and he mistook it for a stage in the life-cycle of *Trypanosoma cruzii*. In 1912 the parasite was given its present name by Delanöe & Delanöe. Wenyon (1926) classified *P. carinii* as a protozoon placing it in the Class Sporozoa, and although it is still regarded as such by the majority of parasitologists, others, notably Csillag & Brandstein (1954), considered it should be classed as a fungus and placed among the Saccharomycetes.

Pneumocystis pneumonia is an infection which is still endemic in Germany, Poland, Scandinavia, Switzerland and Hungary, though fewer cases are now seen in some of these countries than formerly. In recent years an increasing number of cases have been recognized in North America and small epidemics and sporadic cases have been described in Chile, Australasia and Great Britain. Among the first cases discovered in this country was that described by Baar (1955).

The distinctive chronic interstitial pneumonia, resembling that seen in congenital syphilis, was described by Rössle (1923), and further accounts describing the clinical course of the illness and the pathological changes were given by Ammich (1938) and Benecke (1938). The importance of the disease in endemic areas may be judged from the statement made by Deamer & Zollinger (1953) that in Switzerland over 700 cases had occurred and that the incidence was higher in neighbouring countries.

The disease affects mainly infants, and especially premature infants, during the first six months, and the incubation period is about six weeks. Clinically the illness is characterized by increasing shortness of breath, cyanosis, very little cough, an absence of pyrexia and a normal white cell count in the blood. In several instances the infants have displayed hypo- or agamma-globulinæmia associated with hypoplasia of the lymphoid tissue. Radiologically, the lungs present numerous opacities at an early stage in the illness.

Although predominantly an infection contracted in infancy, an increasing number of cases is being reported in adults and children mainly as a terminal complication of leukæmia, malignant lymphomatous states and in advanced forms of malignant disease. In almost every instance the diagnosis has only been established after death. Pneumocystis infection may also complicate steroid therapy, occurring during the withdrawal of the drugs following a prolonged course of treatment. It has recently been described in a series of patients who died following unsuccessful renal grafting operations (Rifkind *et al.* 1964). In these patients the natural body immune responses had been artificially and purposely reduced to allow successful acceptance of the grafted tissue. In the majority of both the infant and adult pneumocystis infections the natural body immune mechanisms have probably been diminished by immaturity, disease or artificial means and therefore this type of infection qualifies for inclusion among the 'opportunistic' infections.

Macroscopically, the lungs contain extensive pale, greyish-yellow or pinkish, firm, consolidated areas with normal intervening lung tissue and overlying pleura. The consolidated tissue often resembles pancreatic tissue and the septal tissues are prominent and thickened.

Microscopically, there is extensive chronic inflammatory cell infiltration of all the interstitial planes of the lung with lymphocytes and plasma cells. Fibrosis is absent but the alveolar epithelium is often hyperplastic and hyaline membranes may be found. The majority of the alveoli are filled with a foamy, eosinophilic, structureless exudate