REVIEW OF LITERATURE
Coxsackie B virus myocarditis:

Myocarditis of viral origin was first described by Montgomery et al. (1953) who isolated Coxsackie B4 from faeces of three infants with myocarditis in a maternity home in Southern Rhodesia during an epidemic of myocarditis. The virus was also isolated from patients with Bornholm's disease and encephalitis cases prevalent at that time in that area. Van Crevald and de Jager (1956) reported 4 fatal cases of myocarditis in an epidemic of Coxsackie B4 infection in Amsterdam. The virus was isolated from heart muscle of each patient and also from brain in one of them (Verlinde et al., 1956). Kibricke and Benirschke (1956) reported a case of acute myocarditis in a newborn who also developed meningo-encephalitis and Coxsackie B3 was isolated from faeces.

Fletcher and Brennen (1957, 1958) first reported a case of pericarditis due to Coxsackie B1 in an adult. Since then, a number of reports of myopericarditis both in adults and children due to Coxsackie B viruses have appeared in literature. Myocarditis in a newborn infant with encephalomyelitis due to Coxsackie B4 was reported by Delaney and Fukunga (1958). The virus was isolated from heart tissue. Naudé et al. (1958) isolated Coxsackie B3 from heart tissue in a fatal case of neonatal myocarditis.
Association of Coxsackie B5 virus with benign pericarditis was described by Gillet (1959). In two cases, this virus was isolated from faeces with serological rise in neutralising antibody titre while in two other cases, there was only serological evidence of the virus infection. Null et al. (1959) also found this virus associated with pericarditis in three cases. Brodie and Marchessault (1960) isolated Coxsackie B virus from pericardial fluid, but the virus type was not determined. Myocarditis and pericarditis associated with Coxsackie B5 virus have been reported by other workers also during this period (Connolly, 1961; McClean et al., 1961; Hedlund et al., 1962; Strom, 1962 and Pollen, 1963). Among four cases of Coxsackie B5 infection reported by Babb et al. (1961), two were associated with myocarditis, third with myocarditis and croup and the fourth with croup only. A case of myocarditis due to Coxsackie B4 was described by Swann (1961). The patient also developed pleurodynia and orchitis.

Johnson et al. (1961) found evidence of Coxsackie B virus infection only in one out of 34 cases of acute benign pericarditis occurring outside Coxsackie virus epidemic period. Two fatal cases of neonatal myocarditis with generalised infection of Coxsackie B2 were described by Robino et al. (1962). The virus was isolated from throat washings, faeces, blood, myocardium and CSF in one of the cases and from myocardium in another. Monaldi et al. (1963) isolated Coxsackie B2 from pericardial fluid in case of pericarditis.
In a serological investigation done in 24 sporadic cases of myocarditis in Glasgow during 1960 to 1963, six cases showed evidence of recent Coxsackie B virus infection (Middleton and Grist, 1965). A fatal case of myocarditis due to Coxsackie B4 in a 13 year old girl was described by Sanyal et al. (1965). Isolation of the virus from pericardial fluid and the presence of a high homologous serum neutralising antibody titre suggested the diagnosis.

Jennings (1966) reported a fatal case of myocarditis with cardiomegaly in a 14 day old infant. Coxsackie B5 was isolated from intestinal content of the body at autopsy and subsequently from the faeces of the mother also. Ten cases associated with Coxsackie B virus infection with development of myocarditis and/or pericarditis were described by Smith (1966), who suggested that they be better termed as myopericarditis. Sulton et al. (1967) reported a fatal case of myocarditis in a 42-year old man who developed muscle pain and breathlessness which increased after he went for swimming, rapidly developing into a fatal heart failure. Coxsackie B4 was isolated from heart tissue.

During the outbreak of a Coxsackie B5 infection in Europe, many cases of myocarditis associated with this virus infection have been reported. From Finland, Helin and Colleagues (1968) reported on 18 cases manifesting heart disease. They comprised of 33% of the epidemic illnesses admitted in their hospital. The patients developed myocarditis or pericarditis or both and were mostly adults.
In United Kingdom, 5 percent of 900 persons with Coxsackie B5 infection during the epidemic had cardiac disease (Report, 1967). Grist and Bell (1968) in Glasgow area found evidence of Coxsackie B5 infection in 8(15 percent) of 53 cases of acute cardiac or pleurodynia like illnesses during this epidemic. In studies on sporadic cases, during 1963-65, Bell and Grist (1968) found evidence of Coxsackie B virus infection in 12 of 40 cardiac illnesses. Berkovich et al. (1968) in their study of acute non-rheumatic myocarditis found association of Coxsackie B4 in one case, Coxsackie B5 in another and a third showing serological evidence of Coxsackie B1, B3 and B4 infections.

Sainani and his colleagues (1968) in a series of 57 cases of suspected cardiac illnesses found 22 of them associated with Coxsackie B virus infection. There were 13 men and 9 women with ages ranging between 15 and 66 years. There were ten cases of pericarditis, 10 of myocarditis and 2 with features of both. The virus types associated with, were Coxsackie B1 in one case, B2 in six cases, B3 in three cases, B4 in nine cases and B5 in 3 cases.

Van Loon and Masson (1968) in their investigation of 100 cases of pericarditis found 2 cases associated with one each of Coxsackie B3 and B5 infections. Myopericarditis associated with Coxsackie B2 in a 49-year old male was described by Mathews et al. (1970). The patient developed constructive pericarditis and after thoracotomy, adherent pericardium was successfully removed. Dawson and Rogen (1970)
reported association of Coxsackie B5 in two cases and Coxsackie B4 in another case.

In a retrospective study, Koontz and Ray (1971) found that 20 of 45 patients with myocarditis had serological evidence of Coxsackie B virus infection. Grist (1972) in a study during 1959-67 found 23 cases of acute cardiac disease having acceptable evidence of enteroviral aetiology and among these 17 were due to Coxsackie B viruses.

Woods et al (1973) virologically investigated 257 adults with acute cardiac disease and found 31 associated with Coxsackie B viruses. Virus types associated with were Coxsackie B2 in four cases, B3 in ten cases, B4 in eleven cases and B5 in six cases. Only in five cases virus could be isolated.

In a six-year study, Grist and Bell (1974) investigated 385 patients with suspected heart disease and 26 patients with Bornholm's disease for association with virus infection. The criteria for association of the virus to the disease were isolation of virus with serological response, serological evidence as shown by rise or fall in antibody titre and antibody titre in a dilution of 1:256 and above. Apart from 65 percent of Bornholm's disease, 49 percent of myocarditis, 30 percent of pericarditis and 10 percent of other cardiac and non-cardiac group were associated with virus infection. Atleast half the cases of acute myocarditis and one third cases of pericarditis were
associated with Coxsackie group B virus infections. The associations of virus infection was most frequently found in children below 10 years and infrequent in adults above 50 years.

In Thailand, Ayuthya et al (1974), in a four year period of study from 1969-1973, on the basis of serological study found that 5 of 12 infants and children with primary myocardial disease were associated with Coxsackie B virus infection. Coxsackie B3 and B4 were associated with 2 and 3 cases respectively.

Michalis and Thomas (1977) virologically investigated 38 patients with clinical diagnosis of acute myocardial infection. Ten had serological evidence of Coxsackie B virus infections; virus types being Coxsackie B2 in one case, Coxsackie B3 in 6 cases; Coxsackie B4 in one case and Coxsackie B5 in two cases. Both the cases associated with Coxsackie B5 also had evidence of influenza A virus infection.

In India, there are very few reports on virological investigations done on cases of myopericarditis. Agarwal et al (1970) were the first to report a case of Coxsackie B3 virus myocarditis in a child in Chandigarh and they established the diagnosis by isolation of the virus in faeces and throat swab along with serological evidence of rise in neutralising antibody titre. Sainani et al (1975) from Nagpur reported 19 cases of myocarditis associated with Coxsackie B virus. Viruses implicated were Coxsackie B2 in two cases.
Coxsackie B3 in four cases, Coxsackie B4 in eight cases and Coxsackie B5 in five cases. In 9 cases, viral association was proved by isolation of virus along with demonstration of four-fold rise in neutralising antibody titre and in other 10 cases only by rise in antibody titre.

Myocarditis associated with enteroviruses other than Coxsackie B viruses:

Enteroviruses other than Coxsackie B viruses have also been often reported as associated with heart diseases. Jungeblut and Edwards (1951) isolated poliovirus from the myocardium of a fatal case of interstitial myocarditis. Hildes et al (1955) showed histological evidence of myocarditis in 40 to 90 percent of fatal cases of poliomyelitis.

Association of ECHO viruses with heart diseases have also been reported. Kavelman et al (1961) showed serological evidence of ECHO 9 virus infection in a case of pericarditis. They isolated ECHO 19 from faeces in another case but did not find any serological support. ECHO 9 virus infection in a 7-week old boy with myocarditis was described by Chetty et al (1967). They isolated the virus from throat swab and also demonstrated the rise in neutralising antibody titre in the patient. Monif and colleagues (1967) described a fatal case of myocarditis in a 34-year old dentist. ECHO 9 was isolated from myocardium.

Van Loon and Masson (1968) in their study of 900 cases of pericarditis found association of Coxsackie A5, ECHO 6
and ECHO 14 in three cases respectively. Berkovich et al. (1968) in their study of acute non-rheumatic myocarditis found one case associated with ECHO 11 virus infection.

Grist and Bell (1969) listed 17 cases of myocarditis associated with enterovirus infections other than Coxsackie B virus. Virus types associated were Coxsackie A1 in two cases, Coxsackie A4 in seven cases including one in which no virological investigation was done but the circumstances suggested infection from his brother; Coxsackie A9 in four cases; Coxsackie A16 in two cases and Coxsackie A23 (ECHO 9) in two cases. In their further studies, Bell and Grist (1970a) reported a case of myocarditis associated with ECHO 19 virus infection. ECHO 9 was isolated from myocardium of fatal case of myocarditis in a 16 year old girl (Peach and Craddock-Watson, 1971). Bell and Grist (1971) recorded one case of pericarditis and 5 case of myocarditis showing evidence of aetiological association with ECHO viruses. ECHO 9 and ECHO 22 were isolated from heart tissue of two patients of myocarditis; ECHO 6 from intestinal contents in one case; ECHO 9 from faeces and throat swab in one case; ECHO 22 from faeces of one case and ECHO 8 from faeces of the case of pericarditis. Five of the patients were infants and one was 34 years old. Lewes (1976) reported six cases of ECHO 9 and one case of ECHO 30 virus infections associated with myocarditis.

Congenital heart disease has also been associated with Coxsackie B virus infection. Brown and Evans (1967) in their
study found that significantly more mothers of infants with congenital heart disease were shown to have experienced infection with Coxsackie B viruses than did matched control women. The most frequently associated viruses were Coxsackie B3 and B4. Most infections were shown to have occurred during first trimester of pregnancy.

Immuno-fluorescent techniques have been employed by Burch and his colleagues to show evidence of association of Coxsackie B virus infection with cardiac diseases. They studied 55 routinely autopsied hearts by means of immuno-fluorescent antibody technique and found Coxsackie B group virus antigens in 17 cases (Burch et al, 1967). A chronic interstitial myocarditis was noted in the cardiac tissue. In another study of 29 heart tissues from infants and children showing interstitial myocarditis, Burch et al (1968) found Coxsackie B virus antigens in 12 cases by the same technique. The virus types associated with were Coxsackie B2 in four cases; Coxsackie B3 in three; Coxsackie B4 in four and Coxsackie B5 in one case.

Schmidt et al (1973) showed the association of Coxsackie B virus infection with cases of pericarditis and myocarditis by demonstration of immunoglobulin M antibody. On sera of 259 patients with clinical diagnosis of pericarditis, myocarditis and pleurodynia, tests for immunoglobulin (IgM) M antibody to Coxsackie group B viruses were performed. Sera of 259 control subjects were also included. 27 percent had IgM antibody as compared with only 8 percent
in control group against different Coxsackie B viruses.

**Other viruses associated with myocarditis:**

Viruses other than enteroviruses have also been implicated in the aetiological relationship to myocardial diseases. A few case reports of myocarditis associated with some virus disease like rubella (Logue and Hanson, 1945), mumps (Goldfinger et al., 1947) and infectious mononucleosis (Hoagland, 1956) have appeared in literature. Most of these were only clinical studies in which myocarditis was noted in the patients during the episode of clinical illness due to the particular virus.

During 1950-56, a serological study using complement-fixation test against influenza A and B was made by Silber et al. (1956) in cases of congestive cardiac failure without any obvious aetiology. They found evidence of infection with influenza A virus in one case, influenza B in three cases and another case of infection with both types. Gibson et al. (1959) in their study during Asian influenza epidemic found electrocardiographic evidence of myocarditis in a number of cases of influenza A virus infection. Woodward et al. (1960) isolated influenza A, Asian type from pericardial fluid of a patient with chronic rheumatic carditis complicated by development of sero-fibrinous pericarditis. Lewes et al. (1974) also found electrocardiographic evidence of myocarditis in cases of proved influenza A virus infection. In 42 proved cases of influenza A virus infections in an outbreak of A2/England/42/72, Verel (1974) found electro-
cardiographic evidence of myocarditis. Grist and Bell (1974) in their study found one among 34 cases of acute myocarditis and another among 44 cases of acute pericarditis associated with influenza A virus infection. The pericarditis case was also associated with higher neutralising antibody titre against Coxsackie B1 and B2 viruses. In another case of acute myocarditis they demonstrated rising complement-fixing antibody titre against influenza C virus but there was significant antibody titres against M. pneumoniae also. Lewes (1976) found evidence of myocarditis in 7 proved cases of influenza A virus infection.

In their investigation of 38 patients with acute myocardial infarction, Nicholls and Thomas (1977) found evidence of influenza A virus infection in eight cases among which two were also associated with Coxsackie B5 virus infection. They could not conclude anything from these findings, since rising titres were equally common in the non-myocardial infarction group.

Cohen (1963) by autopsy findings described measles myocarditis. A fatal case of varicella myocarditis in a 3 year old girl was reported by Tatter et al (1964). At autopsy extensive myocarditis with a few intranuclear inclusion in myocardial cells were found.

A large number of case reports have been published on myocarditis associated with mumps virus infection (Wendkos and Noll, 1944; Rosenberg, 1945; Bland, 1949 and
Horton, 1958) but they have been based on clinical signs and symptoms and electrocardiographic changes in a few patients of mumps and no virological studies had been made in them. Roberts and Fox (1965) reported a case of a 17-year-old patient who died of diffuse myocardial disease after 8 months of illness following mumps. Rise in complement-fixing antibody titres was demonstrated. Thompson and Nolan (1966) described a case of a 9-year-old girl who developed Adams-Stokes syndrome during mumps. Both anti-V and anti-S complement fixing antibodies showed rise in titre.

Adenoviruses have also been found associated with acute myocarditis. Berkovich et al. (1968) isolated adenovirus types 1 and 2 viruses from throat swabs in two cases of acute non-rheumatic myocarditis and they also demonstrated serological evidence of these virus infections in these cases. Grist and Bell (1974) isolated adenovirus type 17 from stool and also showed rise in complement-fixing antibody against adenovirus in a female infant with acute myocarditis. In addition also demonstrated rise in neutralising antibody titre against Coxsackie B3 virus. Nicholls and Thomas (1977) found serological evidence of respiratory syncytial virus infection in one case of acute myocardial infarction among 38 cases which they investigated.

Arboviruses which are highly prevalent in tropical and subtropical areas have also been found associated with myocardial diseases (Obeyesekara and Hermon, 1972, 1973).
They virologically investigated 35 patients who developed myocarditis and cardiomyopathy following dengue and Chikungunya fevers and found evidence of infection suggesting "cause and effect relationship". There were 17 males and 18 females. Three patients died, six completely recovered and two had residual ECG changes. Twenty-six cases developed cardiomyopathy and cardiomegaly. Nagarathnam et al (1973) also reported myocarditis associated with dengue virus infection.

**Experimental myocarditis:**

Most of the experimental work with Coxsackie B virus infection have been carried out mainly in mice. Mice are most susceptible to infection with these viruses during the first 24 hours of life.

Pappenheimer et al (1950) found the development of lesions of the heart in mice inoculated with Powers strain of Coxsackie B4 virus. Melnick and Godman (1951) found myocardial necrosis in 3 of 35 mice (4-5 day old) inoculated with Coxsackie B1 virus and approximately in twice that number of animals if they were inoculated at birth. Histologically there was patchy necrosis followed by fragmentation and hyalin degeneration of cardiac muscle fibres and the lesions occurred in any part of the heart. Kilbourne and Horsfall (1951) showed that adult mice can lethally be infected when cortisone is given to the animal before inoculation with virus. They found prolonged viraemia with presence of virus in different organs like lung, spleen,
liver and pancreas. Kilbourne et al (1956) showed development of gross necrotic lesions of myocardium in cortisone treated adult mice infected with Coxsackie B3 virus.

Grodums and Dempster (1959a) made a detailed study of influence of age factor upon the susceptibility of white mice in experimental infection with Coxsackie B3 virus. Groups of animals at ages varying from 4 days to 182 days were inoculated with the virus. Brain lesions were found in animals of less than 12 days of age and mice inoculated after 12 days of age developed myocarditis. New born mice were not as susceptible to myocardial damage as 12 days old mice and this susceptibility increased up to the age of 23 days and thereafter there was decline, but 6 months old animals were all moderately susceptible (Grodums and Dempster, 1959b). Age of the animal appeared to be a significant factor and other factors such as route of inoculation, sex, virus concentration did not greatly affect the outcome. Heart lesions produced were similar to those described in human myocarditis. They also found that Coxsackie B3 myocarditis could be produced in both young and adult mice regularly without the aid of cortisone. In further experiments, Grodums and Dempster (1962) showed the Coxsackie B3 strains were particularly cardiotropic for 17 day old mice and adult mice as compared to other Coxsackie B viruses. Coxsackie B3 appeared to be the most virulent and residual pathological changes with this virus infection seems to have persisted over a prolonged period of time. Rabin et al (1964) found
weanling mice developed severe myocarditis after infection with Coxsackie B3 (Nancy strain) virus.

Lerner et al (1962) also studied the factor of age and susceptibility of mice to Coxsackie A9 virus infection. Mice varying in age from 1 day to 8 months were inoculated with Coxsackie A9 virus. The virus replicated to a relatively low titres in the hearts of the young (1-40 days old) mice without producing any demonstrable lesions in the heart whereas frank myocarditis with high yields of virus was demonstrated in mice infected at 8 months of age. Lerner and Shaka (1962) found that pathologically new born mice showed only myositis and one year old animal only myocarditis and mice of intermediate ages usually showed both lesions. It has also been shown that in infected mice, Coxsackie A9 virus was isolated in higher titre from hearts of a significantly greater proportion of those that were exercised in the form of swimming than these animals not exercised (Tilles et al, 1964). Gatmaitan et al (1970) repeated these experiments using Nancy strain of Coxsackie B3 virus. Though 25 to 50 percent of the hearts of unexercised animals were affected, the mice did not appear ill and they survived. However, when the mice were made to swim beginning on the first day after infection, most of them died of acute conges-tive failure. Hearts were grossly dilated and almost all the myocardium of the infected, exercised animals was replaced by necrotic infiltrate and the viral titres increased 530 fold.
Burch and his colleagues (1966) showed the development of myocarditis with valvulitis in Coxsackie B3 virus infected mice. The lesions were studied by direct immunofluorescent antibody technique and Coxsackie B4 virus antigen was visualised in affected valves and mural endocardium even after the tissue developed scarring (Sun et al, 1967). Electron microscopic examination of cardiac capillaries in Coxsackie B4 infected mice showed widespread damage of endothelial cells. Particles resembling Coxsackie B virus were seen within the endothelial cells, capillary lumen, interstitial spaces and myocytes (Sohal et al, 1968). These group of workers also produced experimental Coxsackie B4 virus myocarditis in cynomolgus monkeys (De Pasquale et al, 1966). Among the 7 monkeys inoculated with Coxsackie B virus, 6 developed valvular lesions with development of mitral stenosis in 2 and verrucous aortic valvulitis in 2 others. Three of them showed the presence of viral antigen by immunofluorescent antibody test, with the above experimental evidences in mice and monkeys, Burch and his group of workers suggested that atleast some instances of valvulitis in man may be due virus infection rheumatic disease since substantial number of these patients give no history of rheumatic fever.

**Cell-mediated Immunity:**

Forgoing review has shown the importance of Coxsackie B virus infection in the development of myocarditis in man and experimental animals such as mice and monkeys. Heart lesions produced in experimental infection in mice are histologically
similar to those seen in human disease. It mainly consists of destruction of cardiac muscle fibres, infiltration of lymphocytes and mononuclear cells and replacement fibrosis (Longson et al., 1969; Woodruff and Kilbourne, 1970 and Lerner and Wilson, 1973). It has been shown by Wilson et al. (1969) and Fenistone et al. (1973) that myocarditis which develops in weanling mice persists for several weeks and months but infectious virus cannot be isolated from heart tissue after the first week of infection. It is likely, the immunological responses in the animal may play a role in the limitation of the disease process or accentuation of the same.

It is well established that specific immune response of a host is biologically composed of two immune systems: (1) system responsible for cell-mediated immunity and (2) system responsible for antibody production (humoral immunity). It is also well established that the lymphocyte forms an indispensable component of both immune systems. The two central lymphoid organs thymus and Bursa of Fabricius of birds act as sites for production and differentiation of immune component cells. Thymus produces T lymphocytes concerned with cell-mediated immunity and the Bursa of Fabricius of birds B-lymphocytes concerned with antibody production. Mammalian and human equivalent of avian bursa has not been identified, though there is evidence that gut-associated lymphoid tissue could be the bursa analogue in rabbits (Archer et al., 1964).
Cell-mediated immunity encompasses many responses such as blast cell formation, production of many soluble, biologically active molecular mediators and T-cell-mediated cytotoxicity, when sensitised T-lymphocyte comes into contact with the antigen.

Delayed hypersensitivity (DH) is a manifestation of cell-mediated immunity and is characterised by swelling, redness and induration reaching its maximum in 24 to 48 hrs when the antigen is inoculated into the skin (Cell and Banaceraff, 1961). Histologically, there is a mononuclear cell infiltrate of macrophages and lymphocytes. In vitro study of sensitised T-lymphocytes has shown the production of many molecular mediators. Macrophage migration inhibition factor (MIF) is released from sensitised lymphocyte following incubation with specific antigen and acts by inhibiting migration of macrophages from the site of cell-antigen interaction (George and Vaughan, 1962; David, 1968 and Bloom and Bennet, 1970). MIF is just detectable in supernatants of lymphocyte-antigen cultures after 6 hours and is produced continuously for 4 days, after which the cultured cells die (Bennet and Bloom, 1967).

Lymphocyte interaction with antigen also results in production of a chemotactic factor which attracts macrophages (Ward et al, 1971). Macrophage aggregation appears to be related to the disappearance of macrophages from peritonium of a sensitised animal after injection of the antigen (Nelson, 1963) and in vitro, macrophages were observed to clump when
peritoneal exudate cells from sensitised animals were mixed with antigen (Lolekha et al, 1970). Some of the other important molecular mediators released from sensitised T-lymphocytes on contact with specific antigen, are blastogenic factor (Kasakura and Lowenstein, 1965); lymphotoxin which destroys cells in tissue culture (Williams and Granger, 1969) and macrophage activating factor which induces increased membrane activity and stickiness in macrophages (Nathan et al, 1971).

Basically there exists three modes of infection by pathogenic organisms (Mudd, 1970), which are characterised by (1) an acute and usually short lived illness, (2) a chronic illness in which the invading organism is capable of intracellular growth and (3) a latent or steady state infections which are primarily viral. Resistance of the host against intracellular organisms such as fungi, protozoa, viruses and certain bacteria is dependent on cell-mediated immunity (Henry and Goldman, 1975). Actually, the expression of true cellular immunity ultimately depends upon the metabolic and functional activity of activated macrophages (Mackaness, 1970). The macrophages of immune animals have been shown to be activated to increase resistance against many bacterial agents (Lurie and Denneberg, 1965; Elberg et al, 1957; Mackaness, 1969; Patterson and Youmans, 1970; Godal et al, 1971 and Halliburton and Blaskovic, 1975).

But its role in viral infections is less clearly established though it has been shown that macrophages do have a role in limiting the spread of viruses and that this particularly applies to virulent strains (Allison and Mallucci, 1965).
Although much data is not available concerning the role of macrophages in viral infections in man, some experimental evidences are available to suggest that macrophages may be a critical factor in viral infections. Mims (1964) in his review on role of reticulo-endothelial system cells, showed a correlation between the resistance of macrophages to viruses and resistance of the animal to the particular virus. It has been shown that virulence of ectromelia virus depends on its capacity to grow in mouse macrophages (Roberts, 1964). Goodman and Koprowski (1962) have shown that group B arbovirus could be grown in macrophages of susceptible strain of mice but not in resistant strain. Macrophages from immune animals have been shown to have increased resistance to vaccinia virus (Tompkins et al, 1970).

The importance of cell-mediated immunity in resistance to viral infections has been well reflected in studies of certain clinical conditions in man with certain immune deficiency diseases. Patients, with severe but uncomplicated hypogamma-globulinaemia, react normally to live vaccinia virus used in small pox vaccination (Wilson and Miles, 1975a). Nahmias et al (1967) reported a fatal case of measles in a 4-month old girl who had normal levels of immunoglobulins but had thymus aplasia and almost complete absence of small lymphocytes. A progressive case of vaccinia was described by O'Connell et al (1964) in a patient with normal humoral immune response but defective
cellular immunity. After failure of immunoglobulin treatment, transfer of leucocytes from an immune donor resulted in improvement and development of positive skin test to killed vaccinia virus. Similar observation was also made by Hanson et al (1966) in a case of vaccinia gangrenosa in a child with normal humoral antibodies.

Another group of patients who present themselves with decreased resistance to viral infections are, those receiving immunosuppressive drugs or with lymphomas such as Hodgkin’s and other diseases resulting in deficiency of cell-mediated immunity. Graighead et al (1967) showed that 73% allografts recipient patients developed cytomegalovirus infection because of immunosuppressive drugs given to them. In an analysis of 60 cases of death after transplantation, 30 patients were found to have evidence of cytomegalovirus infection while one other case had viral hepatitis and another Herpes Zoster (Editorial, 1967). Schwartz (1969) reported development of Herpes virus pneumonia in patients receiving antilymphocyte sera. Hodgkin’s disease is associated with thymic function deficiency and it has been found that Herpes virus group, particularly Herpes Zoster, cause generalised infections very frequently (Glasgow, 1970). In certain congenital diseases in which cell-mediated immunity is defective, virus infection is a recurring and often fatal complication. Progressive, generalised vaccinia is common in many of these conditions. Fulgiriti et al (1968) described progressive generalised vaccinia in Nezlof’s syndrome.
in which antibody production is substantially normal.

Experimental studies have also been made to study host resistance to virus infections after using immuno-suppressive regimens, such as thymectomy, X-irradiation, antithymocyte serum and immuno-suppressive drug therapy. Miller (1961), in a classical experiment of thymectomy in neonatal mice, showed development of severe impairment of cell-mediated immunity in the animal. He also was able to show that even in adult mice, if sublethal irradiation preceded thymectomy, similar immune defects could be produced (Miller, 1962). In both the above types of animals, cell-mediated immunity could be restored by thymus grafting, infusion of lymphoid cells and by thymic extracts (Miller and Osaba, 1967). In such experimentally thymectomised animals enhanced susceptibility to several virus infections has been reported. Antilymphocyte serum has also been found to enhance susceptibility to virus infections (Hirch and Murphy, 1968). Increased susceptibility of adult mice to intraperitoneal infection in Herpes virus type has been reported to occur after treatment with suppressant of macrophages and lymphocyte function (Zisman et al., 1969) and neonatal thymectomy (Mori et al., 1967). Zisman and Allison (1976), using cyclophosphamid treated mice, obtained results which indicate that protection of mice against Herpes virus type 1 is predominantly T-lymphocyte dependent and suggests that antibody dependent cell-mediated immunity may also play a role in vivo.
Woodruff and Woodruff (1974), in experimental infection of mice with Coxsackie B3 virus, showed that immunologic responses influence the development of cardiac lesions, since myocardial inflammation and necrosis were less severe in T-lymphocytes deprived animals (thymectomised, lethally irradiated and bone-narrow reconstituted) than in normal control animals, although virus replicates to high titre in cardiac tissue in both groups. They suggested that reaction mediated by T-lymphocytes might be involved in the destruction of myocardial cells. Therefore, they made a study of the generation of cytotoxic effector cells in mice infected with Coxsackie B3 virus using radiochromium assay system with virus infected and uninfected syngeneic neonatal fibroblasts as target cells (Wong et al., 1977a). It was found that virus specific cytotoxic spleen cells occurred in highest numbers on the 7th day after infection and declined by days 12 to 14. It was also found that the effector cells in this system were thymus-derived lymphocytes indicating that infection in mice with Coxsackie B3 stimulates production of cell-mediated immunity (Wong et al., 1977b). In addition, it was shown that virus infected neonatal myocardial cells were susceptible to cytotoxic activity of virus-immune spleen cells.