COXSACKIE B VIRUS INFECTION OF THE NEWBORN

ROBERT E. FECHNER, M.D.; MARGARET G. SMITH, M.D., AND J. NEAL MIDDELKAMP, M.D.

From the Departments of Pathology and Pediatrics, Washington University School of Medicine and the St. Louis Children's Hospital, St. Louis, Mo.

Coxsackie group B viruses have been known to produce a variety of clinically apparent illnesses. Among these are pleurodynia, aseptic meningitis and pericarditis, which are usually self-limited and without sequelae or mortality. In contrast, infection by Coxsackie B in newborn infants is frequently fatal, with myocarditis and usually meningoencephalitis present at necropsy. Since the reports of Javett and colleagues[1] and of Montgomery, Gear, Prinsloo, Kahn and Kirsch[2] in South Africa first indicated that these viruses were the cause of fatal infections in a group of infants, similar small epidemics have been reported, particularly from Europe,[3-6] and a number of individual cases have been observed in this country.[7-15]

This paper presents the histories and necropsy examinations of 6 infants who died in St. Louis between August 23 and October 20, 1960. In 3 instances, Coxsackie virus, group B, type 4, was isolated from tissue obtained at necropsy. The distribution and character of the histologic lesions in the organs of the other 3 infants so closely resembled those in the 3 from which the virus was isolated that they also are regarded as Coxsackie B infections.

REPORT OF CASES

Case 1

This 9-day-old white boy was admitted to St. Louis Children's Hospital on September 28, 1960, and expired 6 hours later. He was full-term, born to a 21-year-old mother whose pregnancy and delivery were normal. On the third post-partum day, the mother had pyuria. The infant's first 7 days of life were uneventful, except for mild fever on the fourth day which rapidly subsided without therapy. On the eighth day, he refused feedings and developed severe respiratory difficulty.

On transfer from another St. Louis hospital the child had a temperature of 35° C., and there was respiratory distress. He was lethargic, cyanotic, and had a bulging but soft fontanel. Spinal fluid examination revealed 123 cells per cu. mm. with 95 per cent neutrophils; glucose, 71.0 mg. per 100 ml.; protein, 157.2 mg. per 100 ml. Bacterio-

This work was supported in part by United States Public Health Service Grant No. 2G-897.

Presented in part at the Fifty-ninth Annual Meeting of the American Association of Pathologists and Bacteriologists, Chicago, Illinois, April 27, 1961.

Accepted for publication, October 18, 1962.

logic cultures of the spinal fluid were sterile; throat culture was not remarkable; blood culture grew *Hemophilus influenzae* B. Treatment consisted of antibiotic agents, digitalis, and oxygen. The clinical impression was sepsis and meningitis.

At necropsy the heart did not appear enlarged and was of normal color and consistency. There were scattered foci of atelectasis in both lungs. The heart and lungs together weighed 115 gm. (normal combined weight, 75 gm.). The unfixed brain weighed 475 gm. (normal weight, 390 gm.). The vessels of the meninges were moderately congested but the meninges were transparent. Coronal sections of the cerebral hemispheres and brain stem disclosed no further abnormalities. Other organs were normal.

Blocks of the left ventricular myocardium and of liver and a wedge of the cerebral cortex were stored at −20° C. for virus isolation.

Bacteriologic cultures of the blood, a swab of the lung, and a swab of spinal fluid were sterile.

Microscopically, the significant pathologic lesions were in the heart and brain. In the heart there was a dense but patchy interstitial inflammatory exudate composed largely of mononuclear cells with occasional neutrophils (Fig. 1). Areas of myocardial fiber necrosis were present (Fig. 2). These changes were most marked in the left ventricle. In sections of the right ventricle, there was only a slight interstitial infiltration.

Over the cerebral cortex and brain stem there was a slight meningeal exudate of large mononuclear cells with a few lymphocytes and an occasional neutrophil. Parenchymal lesions were not evident in sections from the cerebral cortex or cerebellum. Small focal collections of large mononuclear cells were seen near the aqueduct of Sylvius in the mesencephalon. Vessels in the pons showed narrow but distinct cuffs of large mononuclear cells and a few lymphocytes. Microscopic sections of medulla and spinal cord were normal.

Anatomic Diagnosis. Myocarditis; meningoencephalitis, slight; germinal center necrosis in splenic follicles; focal pulmonary atelectasis with intra-alveolar hemorrhage; fatty metamorphosis of liver, slight.

Case 2

A 6-day-old white girl was admitted to St. Louis Children's Hospital on October 8, 1960, and expired 26 hours later. She was the product of a 7½ month pregnancy, weighing 6 pounds, 9 ounces at birth. The 20-year-old mother had fever and pyuria for 1 week prior to delivery. At 2 days of age, the infant developed fever of 102° F., with pulmonary infiltration revealed by roentgenogram. The infant was treated with antibiotic agents, but the fever persisted until the fifth day of life when she suddenly became gray, cold and lethargic.

On transfer from a Troy, Missouri, hospital (50 miles from St. Louis) the child was pale and flaccid; temperature, 36.2° C. There was marked tachycardia, tachypnea and absent Moro and sucking reflexes. Spinal fluid contained 289 cells per cu. mm., predominantly mononuclear cells; glucose, 19 mg. per 100 ml.; protein, 139 mg. per 100 ml. Bacteriologic culture of the blood grew *Hemophilus influenzae* B. The spinal fluid was sterile on culture. Treatment consisted of antibiotic agents and oxygen. The clinical impression was meningitis and sepsis.

At necropsy the heart and lungs together weighed 75 gm. (normal combined weight, 67 gm.). Petechiae were scattered over the epicardium. The myocardium was pale and slightly flabby. There was partial atelectasis of the posterior parts of both lungs. The spleen was moderately enlarged, weighing 13 gm. Other organs were grossly normal, including the brain and spinal cord.

A portion of myocardium was stored at −20° C. Bacteriologic cultures of the blood grew *Aerobacter aerogenes* and a gamma streptococcus which were considered contaminants.

Microscopic sections of the left and right ventricles showed foci of mononuclear cell infiltration and necrosis of myocardial fibers. These lesions were extensive in some areas and negligible in others. In the lungs there was an increased number of lymphocytes in some alveolar septums, and the alveolar capillaries were congested.

In the central nervous system, a striking infiltration of the meninges covered the spinal cord and medulla. The exudate consisted predominantly of large mononuclear cells with many lymphocytes and rare neutrophils. However, the meninges over the cerebral cortex contained only a few large mononuclear cells. There was a perivascular infiltrate of large mononuclear cells about a few small vessels in the cerebral cortex but no other parenchymal lesions. In contrast, the inferior olivary nuclei contained several dense collections of cells consisting predominantly of large mononuclear cells, some of which were apparently microglial in origin (Fig. 3). Ganglion cells adjacent to the inflammatory reaction were undergoing degeneration.

Anatomic Diagnosis. Myocarditis; petechiae of epicardium; meningoencephalitis; focal pulmonary atelectasis; interstitial pneumonitis, slight; follicular hyperplasia of spleen, slight.

Case 3

A 7-day-old white boy was admitted to St. Louis Children's Hospital on August 23, 1960, and expired 7 hours later. The child was full-term, born to a 23-year-old mother whose pregnancy was complicated by a "viral" infection beginning several days prior to delivery. The father and a sibling of the infant also had a "viral" infection similar to that of the mother. On the sixth day of life the infant developed anorexia, hypotonia, became pale and had a feeble cry.

On transfer from another St. Louis hospital, the infant had a temperature of 36° C., and there were tachycardia and tachypnea. Physical examination revealed cardiomegaly and a systolic murmur, edema of the lower extremities, and hepatomegaly. He was treated with antibiotic agents. The clinical impression was sepsis.

At necropsy no significant gross abnormalities were noted. Bacteriologic culture of blood was sterile.

Microscopically, the heart showed multiple small foci of interstitial inflammation. The inflammatory cells were mainly large mononuclear cells, but in some areas, many neutrophils were also present. There were necrotic myocardial fibers in the areas of inflammation. In the lungs, many alveoli were collapsed; others contained erythrocytes and edema fluid. There was centrilobular congestion in the liver with a few focal collections of mononuclear cells within the lobules. The spleen was congested and the germinal centers of the lymphoid follicles contained nuclear debris.

In one focus within the muscularis externa of the small intestine, there was necrosis of the muscle with an infiltrate of large mononuclear cells and a few neutrophils. The overlying mucosa was normal.

In the central nervous system, the meninges over the cerebral cortex and brain stem contained an exudate of large mononuclear cells and a few neutrophils. No parenchymal lesions were seen in the cerebral or cerebellar cortex. However, there were well-circumscribed accumulations of large mononuclear cells in the inferior olivary nuclei and the dorsal nuclei of the pons, in the basilar part of the pons and in a few areas in the white matter of the lateral columns of the spinal cord. In the medulla and pons there was also a perivascular infiltrate.

Anatomic Diagnosis. Myocarditis; petechiae of epicardium; meningoencephalomyelitis; pulmonary atelectasis with intra-alveolar hemorrhage, focal; congestion of liver and spleen; gastric contents in trachea; necrosis and inflammation in muscularis of small intestine, focal.

Case 4

An 8-day-old Negro girl was admitted to St. Louis Children's Hospital on October 10, 1960, and expired 4 hours later. She was born to a 28-year-old mother whose

pregnancy and delivery were normal. The infant had been discharged from the hospital apparently well on the fifth day of life but developed diarrhea the following day. She refused feedings and became lethargic on the seventh day, and the following day had severe respiratory difficulty. On admission to the hospital the child had a temperature of 35° C.; respirations were grunting, and there was no response to painful stimuli. The liver was palpable 3 cm. below the costal margin. A chest roentgenogram showed emphysema and diffuse cardiac enlargement. Blood count revealed a shift to the left, and there were 39 cells per cu. mm. in the spinal fluid, 27 being neutrophils. Bacteriologic cultures of blood and spinal fluid were sterile. Antibiotic therapy was given. The clinical impression was sepsis.

At necropsy the body weighed 2,780 gm. and was 50 cm. in length. The heart did not appear enlarged (weight unavailable). There was slight pallor of the myocardium in the subendocardial part of the left ventricle. A small hemorrhagic area was faintly visible in the septum. A moderate amount of yellow mucoid material was present within the bronchi, but the lungs were otherwise normal. Other organs, including the brain and spinal cord, were grossly normal.

Microscopically, the myocardium of the left ventricle and interventricular septum was intensely congested. Numerous focal areas of infiltrate with mononuclear cells and a few neutrophils were present. Within these foci there was degeneration of myocardial fibers with loss of striations. Near the aortic valve there was an area of myocardial fiber necrosis with extravasation of erythrocytes. One section of the right ventricle showed no inflammation or necrosis.

The lungs contained small foci of intra-alveolar hemorrhage in the right lower lobe. There was marked congestion and precipitated protein in some alveoli, with moderate numbers of macrophages.

The vessels of the leptomeninges were congested and there was a slight mononuclear infiltrate over the parietal cortex and the medulla. The parenchyma of the parietal cortex, of the basal ganglia, hippocampus and cerebellum was normal. Mononuclear cells surrounded several vessels in the parenchyma of the medulla and a small accumulation of mononuclear cells was present immediately adjacent to the inferior olivary nucleus. The spinal cord was normal.

Anatomic Diagnosis. Myocarditis; meningoencephalitis, slight; congestion of lungs.

Case 5

A 25-day-old white boy was admitted to St. Louis Children's Hospital on October 18, 1960, and expired 3 days later. He was born after 8 months' gestation to a 20-year-old mother. Delivery was by Caesarean section because of a placenta praevia. Weighing 2,140 gm. at birth, he had persistent mild respiratory distress and failed to gain weight for the first 2 weeks of life. The mother received treatment for a post-partum "kidney infection." When 24 days of age, the infant refused feedings and became lethargic. Spinal fluid examination revealed 200 cells per cu. mm., 90 per cent being mononuclear; glucose, 54 mg. per 100 ml.; chloride, 112 mg. per 100 ml.

On transfer of the infant from another St. Louis hospital, the temperature was 35° C.; tachycardia and Cheyne-Stokes respirations were manifest. The liver and spleen were both palpable, 1 cm. below the costal margin. Bacteriologic cultures of blood and spinal fluid were sterile. The infant received antibiotic therapy and digitalis. The clinical impression was meningitis.

At necropsy the body weighed, 2,080 gm. and was 47 cm. in length. The heart muscle was pale but no other abnormality was noted. The lungs contained areas of atelectasis and a small amount of clear mucus in the trachea. The heart and lungs together weighed 55 gm. (normal weight, 59 gm.). There were 5 cc. of clear fluid in the peritoneal cavity. The brain and spinal cord were grossly normal.

Cultures of blood grew Proteus and a staphylococcus, type unspecified. A culture made from the pleura grew a gamma streptococcus and *Aerobacter aerogenes*. A culture made from the surface of the brain grew an unspecified Proteus species.

Microscopically, sections of both atriums and both ventricles of the heart disclosed patchy foci of necrosis with an infiltrate predominantly of large mononuclear cells. There was a similar infiltrate in the epicardium. In the lungs the alveolar septums were slightly thickened by a uniform interstitial infiltrate of lymphocytes and large mononuclear cells, and the septums were moderately congested. Foci of atelectasis and small areas of intra-alveolar hemorrhage were present. There was marked congestion of the pancreas.

A moderate mononuclear exudate was present in the leptomeninges. This was patchy in distribution, most marked over the brain stem, and less severe over the cerebral hemispheres and spinal cord. In a section of the precentral gyrus, a focal infiltrate of large mononuclear cells with a few neutrophils was present in the intermediate layers of the cortex. The motor cortex was normal. There was a perivascular infiltrate of large mononuclear cells in the basal ganglia and pons, and to a lesser extent in the thalamus. Focal collections of these mononuclear cells occurred within the inferior olivary nuclei, and similar but smaller foci were found in the parenchyma of the basilar and dorsal portions of the pons. The choroid plexus of the fourth ventricle was congested and infiltrated with large mononuclear cells.

A few small aggregates of large mononuclear cells were present within the anterior horns of the spinal cord, without alterations in the ganglion cells. There was an infiltrate about only a few small vessels.

Anatomic Diagnosis. Myocarditis; meningoencephalomyelitis and ependymitis; pulmonary atelectasis; interstitial pneumonitis, slight; peritoneal effusion, slight; fatty metamorphosis of liver, slight.

Case 6

A 9-day-old white girl was admitted to Cardinal Glennon Hospital on October 11, 1960, and expired several hours later. The pregnancy and delivery at term were uncomplicated except that the mother had an upper respiratory infection for a week prior to delivery. At 3 days of age, the infant had fever of 101.6° F., tachycardia and pharyngitis. Chest roentgenogram showed slight pulmonary congestion. She received antibiotic agents. The tachycardia persisted and she was then given digitalis.

After the baby was transferred from a hospital in Collinsville, Illinois (about 15 miles east of St. Louis), the temperature was 99.4° F. There was neither tachypnea nor tachycardia; death occurred before a diagnosis could be established.

At necropsy the pericardium contained an estimated 10 cc. of fluid. The heart weighed 27 gm. (normal 22 gm.). No other abnormalities except epicardial petechiae were observed. The lungs were slightly firm and congested. The spleen was somewhat enlarged, weighing 18 gm. The unfixed brain weighed 400 gm. (normal, 430 gm.). The gyri were flattened and the white matter of the basal ganglia, brain stem and cerebellum was focally congested.

Bacteriologic cultures of blood and lung were sterile. Blocks of tissue from brain, heart, lung, liver, pancreas, kidney and spleen were saved for viral cultures.

Microscopically, there was a widespread but patchy interstitial inflammation of the myocardium like that in the 5 previous cases. The mononuclear cells extended into the epicardium, and the vessels of the epicardium were congested.

There was severe congestion and focal atelectasis of the lungs. Foamy histiocytes and squamous epithelium were present within many alveoli. The pancreas was extremely edematous, and there were a few small foci of hemorrhage. In these hemorrhagic areas, mononuclear cells and neutrophils were present in small numbers. No abnormalities of the parenchymal cells were evident. Except for congestion of vessels, sections of the other abdominal organs were normal.

The meninges of the cerebral hemisphere and brain stem were infiltrated with many large mononuclear cells. In the cerebral cortex underlying a particularly severe focus of meningitis, a loose aggregate of mononuclear cells and neutrophils was present. Within the white matter of the temporal lobe were dense, sharply circum-

scribed accumulations of large mononuclear cells and lymphocytes, and a perivascular infiltrate. Examination of the hindbrain was limited to a section of medulla and one of cerebellum. No parenchymal lesions were present in these sections.

Anatomic Diagnosis. Myocarditis; meningoencephalitis, slight; pulmonary congestion and focal atelectasis; congestion of abdominal viscera; edema and focal hemorrhage of pancreas.

Virus Isolation

Previously frozen material from the myocardium, cerebral cortex, and liver in case 1; myocardium in case 2; and myocardium, brain, kidney, spleen, lung, pancreas and liver in case 6 were triturated and inoculated into cultures of monkey kidney and HEp-2 cells. Coxsackie B4 virus was isolated from the myocardium of cases 1 and 2 and myocardium, brain, kidney, spleen, lung and pancreas of case 6. No virus was isolated from the cerebral cortex and liver of case 1 or the liver of case 6.

Discussion

A fairly well characterized pathologic pattern of Coxsackie B virus infection in infants has emerged from previous reports. This is myocarditis, usually some degree of meningoencephalitis and, less frequently, involvement of other organs. The gross necropsy findings in the cases presented here did not reflect the severe changes found on microscopic examination. Certainly, there was nothing specific to indicate a Coxsackie virus infection. The most constant changes were in the myocardium. Grossly, there was pallor of the myocardium in 3 instances and petechiae in 4. Cardiomegaly has been recorded in the majority of published reports. However, this was not our experience. Since the heart and lungs were weighed as a unit, it was not possible to detect cardiomegaly of slight degree. However, the combined weights of the heart and lungs did not differ significantly from the normal, and in no instance did the heart appear enlarged. Microscopically, the characteristic lesion was necrosis and interstitial inflammation of the myocardium. This was extensive but patchy in distribution. In two cases, the left ventricle was considerably more involved than the right. Such a distribution has been noted by others.[7,16] In case 4, the right ventricle was so minimally affected that it would have been possible to overlook the slight inflammation, had one not been alerted by the severe changes in the left ventricle. This emphasizes the necessity of taking several blocks from different chambers of the heart in infants suspected of having a myocarditis. In one laboratory, it was not possible to find histologic lesions in at least one block of the myocardium from each of 4 infants with Coxsackie B3 infection. However, systematic examination of all 4 chambers ultimately disclosed lesions in each one.[16] Also, in young cynomolgus monkeys experimentally infected with Coxsackie B4 virus, the myocardial lesions were predominantly left ventricular.[17]

The heart has been the organ from which virus has been isolated most

frequently. This is in part a reflection of the more frequent attempts to isolate virus from this organ in cases of sudden death or sepsis of unknown cause. There is evidence, however, that in a generalized infection, the myocardium can yield higher titers of virus than other organs. Dömök and Molnar [4] found by titration that the myocardium yielded virus in a concentration 1,000 times that found in brain, liver, spleen, pancreas and lung of the same case. Similar results have been found by others.[8,18] In addition, it had been demonstrated that Coxsackie B3 virus inoculated into the brain of mice resulted in higher concentrations in the heart than in the brain of animals killed 1, 2 and 5 days after inoculation.[18]

The peculiar susceptibility of the infant myocardium to Coxsackie B virus infection is entirely unexplained. Clinically, cardiac involvement in older children and adults is usually limited to the pericardium. There have been, however, several cases of clinically diagnosed myocarditis with rising serum-antibody titers to various types of group B virus. These patients have ranged in age from 5 [11] to 35 years.[19–21] Fatalities have not been reported among these older patients. Indeed, with rare exceptions, all fatal cases have been within the first 4 weeks of life. Kagan and Bernkopf [22] alluded to isolation of Coxsackie B3 virus from the myocardium of a 10-month-old child but gave no further details. B4 virus has been isolated at necropsy from the myocardium of a 7-week-old infant [15] and of an 8½-week-old infant.[13] All of our patients were less than 28 days of age.

The lesions in the central nervous system are generally less severe and more variable than in the heart. Grossly, the only change in our cases was the congestion of the meningeal vessels in one and of the cerebral vessels within the brain in another. An area of subarachnoid hemorrhage in case 5 was interpreted as the result of a postmortem cisternal puncture. Other observers have also found minimal gross alterations. Petechiae of the meninges over the mid and hind brain were described by Moossy and Geer [12] in an unusually severe meningoencephalitis due to B3 virus. In another report,[5] the arachnoid was thought to be thickened in the Sylvian fissure and over the pons without a distinct exudate. The majority of cases, however, have no gross abnormality whatsoever.

In the cases presented here, microscopic examination disclosed several lesions of the central nervous system. There was a meningeal exudate composed predominantly of large mononuclear cells and lymphocytes which was most extensive over the brain stem and spinal cord. Perivascular accumulations of cells were seen in the brain stem in 5 instances and in the cerebral cortex in 2. The parenchymal lesions were quite variable in their severity. Only in cases 5 and 6 were focal accumula-

tions of inflammatory cells seen within the brain at a level higher than the mesencephalon. The most constant site was the inferior olivary nuclei. These nuclei were involved in 4 instances. In addition to being the single most frequently affected site, the inferior olivary nuclei were the most severely involved area in those cases in which other parenchymal lesions were present except in case 6. The apparent predilection of the virus for the brain stem and especially the inferior olivary nuclei has been emphasized by Moossy and Geer.[12]

Ganglion cells in areas of inflammation showed moderate degenerative changes. Such changes were also observed in an occasional ganglion cell remote from the inflammatory foci as in the anterior horns of the spinal cord in case 2. Destruction of neurons has been an occasional observation in other reported cases of Coxsackie infection. Degeneration of ganglion cells in the anterior horns with neuronophagia has been described,[12] and degeneration of these cells at all levels of the spinal cord in areas of inflammation but without neuronophagia has been observed.[7] Alterations in ganglion cells of the inferior olivary nuclei have also been recorded.[8,12] Involvement of many parts of the central nervous system has been reported: spinal cord,[7,8,12] medulla,[5,7,8,11,12] pons,[5,7,9,11,12,15,16] cerebellum,[8,9,12,16] subcortical nuclei,[5,8,9,11,12] cerebral cortex,[8–10] choroid plexus,[8,11,12] and meninges.[5,7–12,16]

Since pathologic changes may occur in ganglion cells of the anterior horns of the spinal cord and of the brain stem, the differentiation from acute poliomyelitis is of importance. The alterations in the cells of the anterior horns of case 2 were at levels in which perivascular inflammation of the white matter occurred but inflammatory cells in the gray matter were not seen. Kibrick and Benirschke [8] described slight vacuolation of ganglion cells in the anterior horns without other changes in an infant with Coxsackie B4 infection. When inoculated into suckling mice, virus from this infant produced acute destruction of the ganglion cells of the anterior horns with neuronophagia. This finding is occasionally seen in mice with Coxsackie infections, but does not involve large numbers of neurons or excite a marked inflammatory response.[23] Neuronophagia of slight degree has been reported in a B3 infection.[12] It appears that the lesions of the anterior horns of the spinal cord in Coxsackie infections are neither as severe nor as constant in their occurrence as in poliomyelitis.

The distribution of lesions in the brain stem is a helpful point of differentiation. Bodian has described the predilection of the poliomyelitis virus for the tegmental and medial areas of the brain stem.[24] In contrast, the basilar areas tend to be more involved in Coxsackie infections. Furthermore the frequent involvement of the olivary nuclei, a region spared

in poliomyelitis, is of importance in distinguishing the two infections.

Attempts to isolate virus from the central nervous system have been frequently unsuccessful. In many instances, virus has been isolated from the heart but not the central nervous system.[2,5,6,12] In those cases in which successful isolations of virus from central nervous system tissue have been accomplished,[5,7,8,10,13,15] the only site specifically mentioned has been spinal cord.[7,8,15]

Involvement of many other organs has been reported. Liver,[2,8,11,12,15] spleen,[1,5] adrenal glands,[1,2,7,8,9,12] pancreas,[7,8] lung,[5,8–10] and pituitary[9] have been the sites of significant alterations. Previously, however, no lesion within the intestinal tract has been identified. The focal necrosis and mononuclear infiltration in the muscularis of the small intestine in case 4 is probably on a viral basis since the character of the lesion resembled so closely that observed in the cardiac muscle.

It is interesting that *Hemophilus influenzae* type B was isolated ante mortem from the blood in 2 of these patients. In light of the association of *Hemophilus influenzae* and influenza virus in the pandemic of 1918, the isolation of both *Hemophilus influenzae* type B and ECHO virus type 9 from the cerebrospinal fluid of a 10-month-old infant,[25] and again the association of *Hemophilus influenzae* type B and Coxsackie B4 virus in cases 1 and 2 it is tempting to speculate on the relation of viral infections and the Hemophilus. The lysogenic conversion of *Corynebacterium diphtheriae* from a nontoxigenic to a toxigenic strain by a specific bacteriophage[26] is an excellent example of a virus-bacteria association which produces a severe disease in man. The microscopic pathologic features and viral studies were consistent with a viral infection alone in all of our cases, and we have no specific explanation for the association of *Hemophilus influenzae* type B and Coxsackie B4 virus.

It should be emphasized that combined infections of bacterial and viral etiology may occur, but the rapid and easy isolation and identification of a bacterial agent compared to a virus may prevent one from recognizing the true underlying disease early in its clinical course.

Summary

Six fatal cases of encephalomyocarditis in newborn infants which occurred in the St. Louis area during a 3-month period are reported. Coxsackie B4 virus was isolated from the myocardium in 2 instances and from the myocardium, brain, kidney, spleen, lung and pancreas in another. The pathologic findings were compared with those recorded in other reports of Coxsackie encephalomyocarditis.

REFERENCES

1. JAVETT, S. N.; HEYMANN, S.; MUNDEL, B.; PEPLER, W. J.; LURIE, H. I.; GEAR, J.; MEASROCH, V., and KIRSCH, Z. Myocarditis in the newborn infant. A study of an outbreak associated with Coxsackie group B virus infection in a maternity home in Johannesburg. *J. Pediat.*, 1956, **48**, 1–22.
2. MONTGOMERY, J.; GEAR, J.; PRINSLOO, F. R.; KAHN, M., and KIRSCH, Z. G. Myocarditis of the newborn. An outbreak in a maternity home in Southern Rhodesia associated with Coxsackie group-B virus infection. *South African M.J.*, 1955, **29**, 608–612.
3. LUKACS, V. F., and ROMHANYI, J. Über eine Meningo-Encephalo-Myokarditis-Epidemie bei Neugeborenen, während der Epidemie von Bornholm'scher Krankheit in Ungarn, im Jahre 1958. I. Klinische und pathologische Befunde. *Ann. paediat.*, 1960, **194**, 89–102.
4. DÖMÖK, I., and MOLNAR, E. An outbreak of meningoencephalomyocarditis among newborn infants during the epidemic of Bornholm disease of 1958 in Hungary. II. Aetiological findings. *Ann. paediat.*, 1960, **194**, 102–114.
5. VAN CREVELD, S., and DE JAGER, H. Myocarditis in newborns, caused by Coxsackie virus. Clinical and pathological data. *Ann. paediat.*, 1956, **187**, 100–112.
6. VERLINDE, J. D.; VAN TONGEREN, H. A. E., and KRET, A. Myocarditis in newborns due to group B Coxsackie virus. Virus studies. *Ann. paediat.*, 1956, **187**, 113–118.
7. KIBRICK, S., and BENIRSCHKE, K. Acute aseptic myocarditis and meningoencephalitis in the newborn child infected with Coxsackie virus group B, type 3. *New England J. Med.*, 1956, **255**, 883–889.
8. KIBRICK, S., and BENIRSCHKE, K. Severe generalized disease (encephalohepatomyocarditis) occurring in the newborn period and due to infection with Coxsackie virus, group B; evidence of intrauterine infection with this agent. *Pediatrics*, 1958, **22**, 857–875.
9. SUSSMAN, M. L.; STRAUSS, L., and HODES, H. L. Fatal Coxsackie group B virus infection in the newborn; report of a case with necropsy findings and brief review of the literature. *A.M.A. J. Dis. Child.*, 1959, **97**, 483–492.
10. DELANEY, T. B., and FUKUNAGA, F. H. Myocarditis in a newborn infant with encephalomeningitis due to Coxsackie virus group B, type 5. *New England J. Med.*, 1958, **259**, 234–236.
11. HOSIER, D. M., and NEWTON, W. A., JR. Serious Coxsackie infection in infants and children; myocarditis, meningoencephalitis, and hepatitis. *A.M.A. J. Dis. Child.*, 1958, **96**, 251–267.
12. MOOSSY, J., and GEER, J. C. Encephalomyelitis, myocarditis, and adrenal cortical necrosis in Coxsackie B3 virus infection. Distribution of the central nervous system lesions. *Arch. Path.*, 1960, **70**, 614–622.
13. NEWTON, W. A., JR., and HOSIER, D. M. Coxsackie infection in infants and children: focal and disseminated; fatal and nonfatal. (Abstract) *Am. J. Path.*, 1958, **34**, 587–588.
14. WOODWARD, T. E.; MCCRUMB, F. R., JR.; CAREY, T. N., and TOGO, Y. Viral and rickettsial causes of cardiac disease, including the Coxsackie virus etiology of pericarditis and myocarditis. *Ann. Int. Med.*, 1960, **53**, 1130–1150.
15. KIBRICK, S., and BENIRSCHKE, K. Severe generalized disease in the newborn due to Coxsackie virus group B. (Abstract) *A.M.A.J. Dis. Child.*, 1958, **96**, 498–499.
16. SIMENHOFF, M. L., and UYS, C. J. Coxsackie virus myocarditis of the newborn; a pathological survey of 4 cases. *Med. Proc.*, 1958, **4**, 389–397.

17. LOU, T. Y.; WENNER, H. A., and KAMITSUKA, P. S. Experimental infections with Coxsackie viruses. II. Myocarditis in cynomolgus monkeys infected with B4 virus. *Arch. ges. Virusforsch.*, 1960, 10, 451–464.

18. NAUDÉ, W. DU T.; SELZER, G., and KIPPS, A. Coxsackie virus myocarditis in the newborn. Virus studies. *Med. Proc.*, 1958, 4, 397–401.

19. SWANN, N. H. Epidemic pleurodynia, orchitis, and myocarditis in an adult due to Coxsackie virus, group B, type 4. *Ann. Int. Med.*, 1961, 54, 1008–1013.

20. NULL, F. C., JR., and CASTLE, C. H. Adult pericarditis and myocarditis due to Coxsackie virus, group B, type 5. *New England J. Med.*, 1959, 261, 937–942.

21. CONNOLLY, J. H. Myocarditis during Coxsackie B5 infection. *Brit. M.J.*, 1961, 1, 877–878.

22. KAGAN, H., and BERNKOPF, H. Pericarditis caused by Coxsackie virus B. *Ann. paediat.*, 1957, 189, 44–50.

23. GODMAN, G. C.; BUNTING, H., and MELNICK, J. L. The histopathology of Coxsackie virus infection in mice. I. Morphologic observations with four different virus types. *Am. J. Path.*, 1952, 28, 223–257.

24. BODIAN, D. Virus and Host Factors Determining the Nature and Severity of Lesions and of Clinical Manifestations. In: Poliomyelitis; Papers and Discussions Presented at the Second International Poliomyelitis Conference. J.B. Lippincott, Co., Philadelphia, 1952, pp. 61–87.

25. WRIGHT, H. T., JR., and MCALLISTER, R. M. "Mixed" meningitis: report of a case with isolation of *Hemophilus influenzae* type B and ECHO virus type 9 from the cerebrospinal fluid. (Abstract) Society for Pediatric Research, 32nd Annual Meeting, 1962, p. 107.

26. GROMAN, N. B. Evidence for the active role of bacteriophage in the conversion of nontoxigenic *Corynebacterium diphtheriae* to toxin production. *J. Bact.*, 1955, 69, 9–15.

The authors are indebted to Dr. Drummond H. Bowden, Director of Laboratories, Cardinal Glennon Hospital, St. Louis, for the record and pathologic material of case 6.

[*Illustrations follow*]

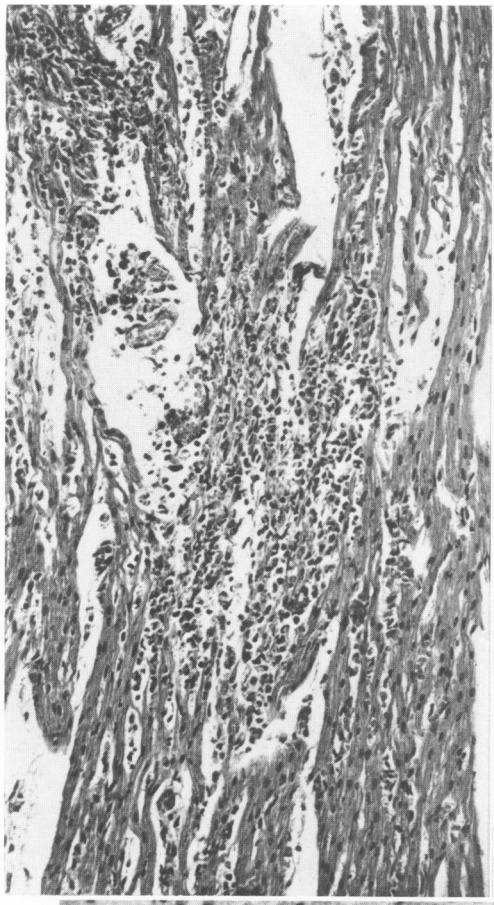
Legends for Figures

Photomicrographs were prepared from sections stained with hematoxylin and eosin.

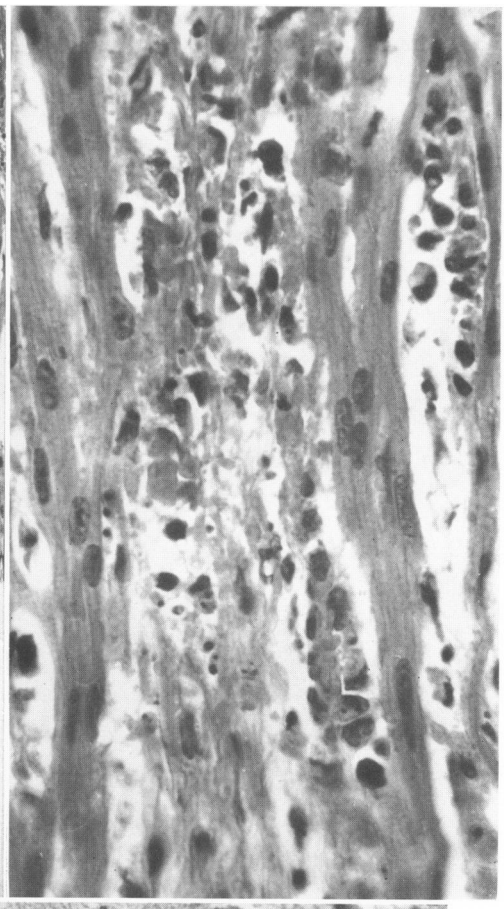
Fig. 1. Left ventricle, case 1. Myocardial necrosis and interstitial infiltration by mononuclear cells are manifest. × 38.

Fig. 2. Left ventricle, case 1. There are fragmented myocardial fibers and infiltration by mononuclear cells. × 150.

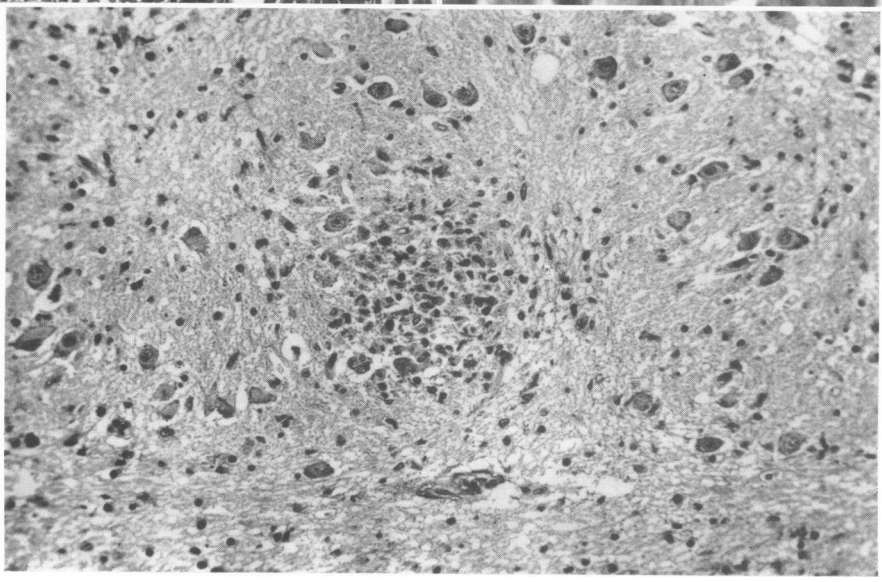
Fig. 3. Inferior olivary nucleus, case 2. A circumscribed collection of mononuclear cells appears within the nucleus. × 72.



1



2



3