by its lofty hills and majestic mountain peaks. It is 101 years ago since Rees, the first settler, came to Queenstown—in February, 1860. In 1861 gold was first discovered in Otago at Gabriel's Gully, and the year following, 1862, there was a rich find near Queenstown, first of all in the Arrow River and later in the Shotover and its tributaries. By December, 1862, there were over 4,000 miners in the Queenstown area. Those of you who have visited this region can in imagination conjure up the scene. The gold was found in and on the banks of turbulent streams in deep rocky chasms with steep precipitous sides. It was impossible to construct roads round those towering cliffs of stone. In summer the miners were blistered by a pitiless sun and in winter they faced ice and snow and flood. They lived in thin calico tents or sod huts or in caves in the rock. Most of them were young and adventurous and tough. But you can imagine the insanitary surroundings, the insufficient and inadequate diet, the plagues of flies. Many died of disease, especially typhoid and diphtheria; many suffered from scurvy and frostbite; and many perished in the dreadful winter of 1863 with its terribly low temperatures and devastating floods. Accidents, many severe, were common and drunkenness was rife.

A hundred years later, as I walked over this country and thought about it, I could not help wondering if there had been any doctor there then. I made it my business to find out. There was, and I am indebted to the late Dr. Fulton for my information. A young Scottish doctor aged 25 arrived in Queenstown in 1862, just before the gold rush. There was at that time no hospital, and his consulting-room was a tent. In all weathers, by day and by night, he rode away into this dreadful mountainous country, tramped up these dark and sinister gorges—often taking his life in his hands, serving these tough adventurers. In the summer sun and in the bitterness of winter he stood beside them and served them. A lesser man would have joined them and become a miner—he knew many were making £200 a week. Some of his profession did. He never deviated from his duty. No doubt some grateful patients paid him handsomely, but it is equally certain that many never paid him at all. He was made a Justice of the Peace and had to combine his medical duties with attempts to preserve law and order in his unruly community.

In 1864 he was made first superintendent of the newly erected District Hospital and continued in that office till 1910. He died in 1911 at the age of 73. After the gold rush he became the principal doctor in the district and a public-spirited citizen. Besides being medical superintendent he was a member of the County Council, President of the Jockey Club, President of the Acclimatization Society, and a patron of the tennis and cricket clubs. His local paper said of him when he died: "During the whole of his professional career Dr. Douglas exercised the greatest medical and surgical skill and performed his duties with much assiduity. Many, many times has the old man ridden in the darkness of the night over the most dangerous and precipitous bridle tracks, into gullies and ravines amidst our gigantic mountains, in prosecution of his profession, knowing full well he would never receive a fee."

Such lives can, I know, be duplicated in the pioneering records of most countries. He would be amazed that I should think his life important enough to describe it to this audience. But in his life he exemplified

the enduring qualities of our profession—a living example of medical ethics. Of such men we in this country are justly proud. Those of you from the United Kingdom can also be proud because you sent him and many more like him to us. And those of you who come from Scotland can be proudest of all because, although born in England, he was of Scottish family and was trained in Glasgow. "By their fruits ye shall know them."

AETIOLOGY OF CENTRAL NERVOUS SYSTEM INFECTIONS DURING PREVALENCE OF POLIOVIRUS AND COXSACKIE VIRUS

SOME CLINICAL MANIFESTATIONS OF COXSACKIE VIRUS INFECTIONS*

BY

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Until recently polioviruses were held responsible for the majority of infections of the central nervous system. They are, however, part of the large enterovirus group which includes also the Coxsackie and Echo viruses, and most members of this group are now recognized as being capable of causing such infections. During 1959 and 1960 virological investigations were carried out on specimens submitted to this laboratory from cases diagnosed clinically as paralytic poliomyelitis, aseptic meningitis, and encephalitis or meningoencephalitis. The findings illustrate the multiplicity of causative agents concerned in these conditions. The commonest during 1959 was poliovirus type 1, whereas in 1960 there was a striking increase in the incidence of Coxsackie virus infection, in particular types B5 and B2. The Coxsackie group B viruses are established causes of epidemic pleurodynia, aseptic meningitis, and neonatal myocarditis, but their full clinical potentialities are still being elucidated. A number of unusual clinical features, including the occurrence of paralysis, are described.

Laboratory Investigations

Virus Isolation

Faecal specimens were obtained from all patients, usually during the first or second day after admission to hospital. These were dealt with at once or kept at -70°C . for 24 to 48 hours. A 20% suspension was prepared with Hanks's solution containing 500 units of penicillin, 200 μg . of streptomycin, and 50 μg . of nystatin per ml. This was centrifuged at 4,000 r.p.m. for 30 minutes. Six tubes, comprising 2 HeLa, 2 human primary amnion, and 2 rhesus-monkey-kidney-tissue cultures, were inoculated with 0.2 ml. each of the supernatant. These were incubated at 37°C . for two hours, and the fluid of each tube was then replaced with fresh medium. The tubes were examined microscopically for cytopathic changes daily for 14 days. In positive cases the fluid was removed and the virus identified by neutralization tests, carried out usually in the type of tissue culture in which it was isolated.

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The virus was diluted 1 in 100 and mixed with equal volumes of antiserum for each of the three types of poliovirus, a pool containing all three polio antisera and a pool of antisera for Coxsackie viruses types B1 to B5 and A9. The antisera were prepared by hyperimmunization of rabbits, and each serum was used at a dilution equivalent to 20 antibody units per 0.1 ml. The mixtures were kept at 37° C. for two hours and 0.2 ml. of each was inoculated into tissue culture tubes. A virus titration was included with each test. The results were read when the control tubes showed 4-plus degeneration, usually within two to three days. When the results were equivocal because of excess virus the test was repeated using approximately 100 TCD₅₀. Viruses which were neutralized only by the Coxsackie antiserum pool were further examined against the individual Coxsackie antisera. Those virus isolates which were not neutralized by either the polio or the Coxsackie sera were tested in the same way against Echo virus antisera types 1 to 20.

Less than 5% of the faecal specimens contained bacterial organisms resistant to penicillin and streptomycin, and these were repeated in the presence of neomycin. A very occasional specimen resisted even this treatment and was filtered through a gradocol membrane.

Destruction of tissue-culture cells within 24 hours by toxic faeces was uncommon when the replacement technique of inoculation was used, and rarely involved all three types of tissue-culture cells. When it occurred either a further specimen of faeces was obtained or a blind passage of the damaged cells was carried out.

The monkey-kidney cells were maintained on medium 199 containing SV₅ antiserum, the HeLa and amnion cells on Earle's saline containing 0.5% lactalbumin hydrolysate and 5% inactivated horse serum. Refeeding of the tubes was carried out at intervals of about five days. All tubes were incubated without rotation.

Sensitivity of Virus Isolation

Monkey-kidney, primary human amnion, and HeLa cells were of equal sensitivity for the isolation of polioviruses. In every case of isolation all three types of cell gave virus growth, but in many cases cytopathic changes occurred 24 to 48 hours earlier in monkey kidney than in amnion or HeLa cells. In a few instances degenerative changes appeared earlier in the latter tissues.

The Coxsackie group B viruses also grew in all three types of cells, but again cytopathic changes in monkey kidney were often in advance of those in either amnion or HeLa cells. This was especially marked in the case

of type B2; in about half of the cases HeLa-cell isolation took three to five days longer than in monkey kidney.

Coxsackie type A9 was readily isolated in both monkey kidney and amnion but not on HeLa cells and the Echo viruses only in monkey kidney.

Serological Examinations

Sera were obtained from patients during the acute and convalescent stages of illness and were stored at -20° C. until used. They were inactivated at 56° C. for half an hour, and both sera from each patient were usually tested at the same time. All sera were examined by complement fixation for antibodies against mumps (V and S antigens) lymphocytic choriomeningitis, herpes simplex, and adenoviruses. Neutralization tests were used for the detection of antibodies against polio, Coxsackie, and Echo viruses. These were carried out by mixing equal volumes of several dilutions of each serum and virus suspensions containing approximately 100 TCD₅₀ per 0.1 ml. They were kept at 37° C. for two hours, and 0.2 ml. of each mixture was inoculated into tissue-culture tubes. The results were read when control virus tubes showed 4-plus degeneration, usually within three to four days. Antibody titres are expressed as the reciprocal of the highest initial dilution of serum producing complete virus neutralization.

Current infection was considered to have occurred only if a fourfold or greater increase in C.F. or neutralizing antibody was demonstrable during the course of illness. In mumps meningitis, however, a V antibody titre of 256 or more associated with an S antibody titre of 64 or more in a single convalescent serum was usually regarded as significant.

Results

Virus Aetiology of Central Nervous System Infections

During 1959.—All the patients with paralysis were clinically diagnosed as cases of paralytic poliomyelitis. As will be seen, this was confirmed virologically in most but not all the cases. Cases described by the physician as aseptic meningitis and non-paralytic poliomyelitis are clinically indistinguishable and therefore only the former term is used. Stool specimens were received from 62 cases of paralytic disease. Viruses were isolated from 53 (84%) (see accompanying Table). These consisted of 52 type 1 and one type 3 polioviruses. Stool specimens were received from 93 cases of aseptic meningitis. Viruses were isolated from 26 (31%). These comprised 18 type 1 and one type 3 polioviruses, five Coxsackie type B4 viruses, and two Echo viruses, types 3 and 9.

Age Distribution of Cases of Paralysis and Aseptic Meningitis

Age in Years	Polio Viruses Isolated		Coxsackie Viruses Isolated		Echo Viruses Isolated	Mumps*	No Viruses Isolated	
	Paralysis	Aseptic Meningitis	Paralysis	Aseptic Meningitis	Aseptic Meningitis	Aseptic Meningitis	Paralysis	Aseptic Meningitis
<i>Virus Diagnosis during 1959</i>								
Under 1	7							2
1-5	30	10		2		2	4	11
6-10	9	3		1	1	2	2	12
11-15	3	3		1	1	1	3	8
Over 15	4	3+3*		1		4		22
<i>Virus Diagnosis during 1960</i>								
Under 1	2		1	2				3
1-5	11			4				8
6-10	2	1	1	9		1		15
11-15	1	1		2	3	2	2	9
Over 15	1	2	2	12		6	1	34

* Diagnosed by serology only.

Serological studies identified a further three cases of type 1 poliovirus infection and nine cases of mumps meningitis. Virus diagnosis was therefore made in 38 cases of aseptic meningitis out of 93 (41%).

During 1960.—Stool specimens were received from 24 cases of paralytic disease. Viruses were isolated from 21 (87%). These were six type 1 and 11 type 3 polioviruses, and four Coxsackie group B viruses—two of type 2 and two of type 5. Stool specimens were obtained from 115 cases of aseptic meningitis, and viruses were isolated from 36 (31%). These were one type 1 and three type 3 polioviruses, 29 Coxsackie viruses, and three Echo viruses, all type 9. The Coxsackie serotypes were B5 isolated from 17 cases, B2 from nine cases, B4 from one case, and A9 from two cases. 10 cases were diagnosed serologically as mumps infection. Virus diagnosis was therefore made in 46 cases of aseptic meningitis out of 115 (40%). Stool specimens were received from 11 cases which were clinically either encephalitis or meningo-encephalitis. Coxsackie type B2 was isolated from one, and two others were diagnosed serologically as caused by mumps virus.

Age and Seasonal Distribution.—The Table shows the distribution by age of the patients examined. During both 1959 and 1960 most cases of poliomyelitis confirmed by virus isolation occurred in children 5 years old and under. In contrast, Coxsackie virus infections were more evenly distributed among the various age-groups, and this applied also to those cases in which no virus diagnosis was made. During 1959, when poliovirus type 1 was predominant, virus isolations were made mainly in the summer and autumn months; 29 type 1 viruses were isolated during May and June, 33 during July to October, but it is noteworthy that eight isolations were also made in the winter months. During 1960 almost all the Coxsackie group B and polio type 3 viruses were isolated during August to October. Most of the polio type 1 isolations (five out of seven) were made in the months previous to this period. In both years the cases of mumps meningitis occurred during June to October.

Coxsackie Group B Infections Involving the Central Nervous System

Most of the cases of aseptic meningitis from which Coxsackie viruses were isolated showed no unusual clinical features. There were fever, headache, malaise, anorexia, nausea, sometimes abdominal pains, and occasionally vomiting. After several days these were followed by the features of meningitis. In only 20% of cases, both children and adults, was there a definite two-stage illness, the primary symptoms being followed by a remission of 12 to 48 hours' duration and then by recurrence of fever with symptoms of meningitis. In only 3 out of 39 cases was there a history of muscle pains. One was that of a 38-year-old woman who had generalized aches and pains for three days prior to the onset of meningitis. The other two cases, in patients aged 20 and 43 years, had severe muscle cramps in both legs at the onset of illness. Relapses are common with Coxsackie infections but in the present series this was noted in only one case in which a 16-year-old boy with aseptic meningitis caused by Coxsackie B2 recovered after eight days but relapsed four days later and was ill with meningitis for another three days.

In most cases the cell counts of the cerebrospinal fluid were between 20 and 175, mostly lymphocytes. The extreme abnormal counts were 9 and 490. The protein

was normal in half the cases, the others showing small increases, usually to between 60 and 90 mg./100 ml. In three cases with typical features of meningitis the findings in the cerebrospinal fluid were completely normal.

A number of features not usually associated with Coxsackie infection were noted in some cases. Two patients from whom type 5 virus was isolated had a rash. One, a 19-year-old woman, showed a pink macular rash which appeared simultaneously with the onset of the symptoms of meningitis. The other was a 9-year-old boy who gave a history of seven days' headache associated with abdominal pains and a generalized macular rash. All these symptoms cleared up and he was well for 24 hours, after which he developed meningitis and a mild conjunctivitis. Conjunctivitis was noticed to occur simultaneously with the onset of meningeal symptoms in two other patients, both children from whom Coxsackie B2 and B5 viruses were isolated.

Paralysis occurred in four cases, and these are described in some detail.

Case 1.—A 5-year-old boy developed fever, headache, and sudden onset of weakness of the right leg. Examination showed neck stiffness and weakness of the flexor and extensor muscles of the affected limb. The cerebrospinal fluid had a cell count of 40, mostly lymphocytes, and 20 mg. of protein per 100 ml. Coxsackie virus type B5 was isolated from the faeces. Homologous neutralizing antibodies increased from <5 to 500 during the course of the illness. There was no increase in antibodies against polioviruses types 1 to 3. This child had received three doses of polio vaccine. He recovered completely from his illness within seven days.

Case 2.—A 20-year-old man gave a history of fever, headache, and pains in both arms for about one week. These subsided for about 24 hours and then weakness of the left arm and hand appeared. On admission he had slight fever and definite weakness of the left arm and wrist muscles. Minimal signs of meningeal irritation were present. The cerebrospinal fluid had 160 cells, almost all lymphocytes, and 65 mg. of protein per 100 ml. Coxsackie B5 was isolated from his faeces and the homologous antibodies increased from 5 to more than 500. Polio antibodies showed no increase during the course of the illness. This patient had received two doses of polio vaccine. At discharge four weeks later there was still some slight weakness of the arm.

Case 3.—A 24-year-old woman gave a history of headache and slight sore throat for 10 days. Three days before admission the headache became intensified and pain appeared in the back of the right leg. Twenty-four hours later she could not walk because of weakness of both legs. Shortly before the onset of her illness her husband had headache and sore throat of two days' duration. On examination there was fever, with stiffness of the neck, and a positive Kernig sign. Both lower limbs showed definite weakness of the flexor and extensor muscles, more pronounced on the right side. The cerebrospinal fluid showed a cell count of 112 lymphocytes and 40 mg. of protein per 100 ml. Coxsackie B2 was isolated from the faeces. Sera were not available for antibody studies. She was discharged after three weeks with slight residual weakness of both lower limbs.

Case 4.—A 9-months-old baby with a history of headache and vomiting for one week was found on examination to have fever of 101° F. (38.3° C.) and head-drop due to weakness of the extensor neck muscles. The lumbar fluid was normal. Coxsackie B2 was isolated from the faeces. Sera were not available for examination. Recovery was complete after two weeks.

The one case of severe meningo-encephalitis seen is described because of its unusual course.

Case 5.—A 38-year-old doctor developed fever up to 104° F. (40° C.) and anorexia but without other symptoms and signs. His children had had an obscure minor febrile illness just previously. He recovered after five days. A week later the same symptoms recurred, lasted two days, and then cleared. Three days later fever and headache developed, lasting for three days and followed by severe mental disorientation with complete retrograde amnesia. Examination revealed evidence of meningeal irritation, and the lumbar fluid contained 176 lymphocytes and 180 mg. of protein per 100 ml. The mental changes lasted six days and then ceased almost abruptly, but were succeeded by facial palsy first on one side and then on the other. These resolved over a period of several days, but troublesome paraesthesiae of the upper and lower limbs were noticed during the next eight weeks. Cocksackie virus type B2 was isolated from the faeces. Serum specimens obtained during the initial illness and the early phase of the stage of disorientation showed a rise of antibodies to Cocksackie B2 from <5 to more than 2,000.

An illness in two siblings presented difficulties in clinical diagnosis and was associated with Cocksackie type B4 infection. The infants, 1 and 2 years old, suddenly developed convulsions followed by fever of 102° F. (38.9° C.) and drowsiness. The older child recovered completely in 24 hours, but the other had fever and was listless for three days. The cerebrospinal fluid was normal and so was the blood picture. Bacteriological examinations of the throat, faeces, and urine showed nothing abnormal. Type B4 Cocksackie virus was isolated from the faeces of both children. Serum specimens obtained from the older child showed a significant rise of homologous antibody.

Cocksackie Group B Infections Not Involving the Central Nervous System

During the course of the Cocksackie epidemic a number of unusual syndromes were detected in infants and small children. These included myocarditis and croup.

Case 6.—The most severe case occurred in a 4-month-old boy. He was admitted with a four-days history of fever, anorexia, malaise, and frequent bouts of screaming. When examined his temperature was 102° F. (38.9° C.) and respiration rate 60 a minute. The fauces were injected and he had conjunctivitis. The heart was enlarged and there was a blowing systolic murmur at all areas with a pulse rate of 160 a minute. The liver was enlarged to two finger-breadths below the costal margin. The next day severe stridor was present and also slight neck stiffness. The respiratory distress responded to oxygen and humidity within 24 hours. The child gradually recovered and after 12 days appeared well although the heart remained enlarged. The clinical diagnosis was acute laryngotracheitis and myocarditis. The cerebrospinal fluid, blood, and urine examinations showed nothing abnormal. A throat swab revealed only normal bacterial flora. The Paul-Bunnell test was negative. The electrocardiogram was normal. Cocksackie B5 was isolated from the throat and a rising titre of homologous antibody occurred during the course of illness. Complement-fixation tests showed no evidence of infection with influenza viruses types A, B, and C, parainfluenza viruses types 1, 2, and 3, or adenoviruses.

A further case of myocarditis without laryngotracheitis was seen in a child aged 10 months from whom Cocksackie B5 was isolated. A third child, 4 months old, with B5 infection had severe croup necessitating tracheostomy; there were no other symptoms or signs, and again serological tests for influenza, parainfluenza, and adenovirus infections were negative. The group of cases presenting myocarditis and croup will be described in greater detail elsewhere (Babb, Stoneman, and Stern, 1961).

Cocksackie B5 infections were also noted in association with respiratory infections in older age-groups. Two of these occurred in girls aged 3 and 12 years; the third case was that of a young house-physician attending cases of Cocksackie infection. The symptoms were low fever, coryza, and cough.

Two cases associated with Cocksackie B5 infection were diagnosed clinically as capsulitis or muscle sprain. These were in boys aged 6 and 10 years, with a few days' history of minor febrile illness followed by sudden onset of pain, in the one case in the hip and in the other in the knee. On examination there was marked limitation of movement and tenderness around the joint, but no other symptoms or signs. Complete recovery ensued after 4 and 10 days respectively.

Cocksackie Group A Infections

During 1960 five cases of infection with Cocksackie A9 were noted. Two of these were cases of aseptic meningitis, but the other three were unusual enough to merit comment.

Two of the three cases were in siblings, 1 and 4 years old. They presented simultaneously with headache, followed after 24 hours by persistent vomiting and diarrhoea which lasted for three days. No other abnormalities were found, but Cocksackie A9 was present in the faeces of both.

Parotid swellings, not due to mumps, have been described as occurring in association with herpangina caused by type A Cocksackie viruses (Howlett, Somlo, and Kalz, 1957). The third case in the present group was that of a 6-year-old boy with aseptic meningitis due to Cocksackie A9. Three days after recovery a left-sided parotitis appeared, lasting for 10 days. A throat swab showed normal bacterial flora, and complement-fixation tests were negative for mumps. The serum amylase was only 5 Wolgemuth units.

Discussion

During 1959 poliovirus type 1 accounted for 88% of all virus isolations from cases of disease of the central nervous system, but this dropped to less than 12% the following year, when Cocksackie virus types B2 and B5 became prevalent. Yearly variation in the incidence of enterovirus types is a characteristic of the group. The suppression of the previously dominant virus is probably determined largely by the altered immune status of the population, but perhaps also by interference. There is evidence of such interference between polio and Cocksackie group B viruses. This has been demonstrated not only in animals (Dalldorf, 1951; Stanley, 1952; Sulkin, Wallis, and Murphy, 1953; Dömök, 1957) and in tissue culture (Le Bouvier, 1954; De Lustig and Brieux, 1957) but also in man. Thus epidemiological studies have shown that during epidemics of Cocksackie type B infections paralytic poliomyelitis is uncommon, and vice versa (Dalldorf, 1955; Dalldorf and Albrecht, 1955). On the other hand, a synergistic relationship may exist between polio and Cocksackie group A viruses, and double infections have been reported from some epidemics, possibly being responsible for increased incidence and severity of paralysis (Melnick, Kaplan, Zabin, Contreras, and Larkum, 1951; Dalldorf, 1952).

Poliovirus is the major cause of paralytic poliomyelitis, and the isolation rate of 84% in the present series is similar to that of others in the United States (Lennette, Magoffin, Schmidt, and Hollister, 1959; Brown, Lenz,

and Agate, 1960; Meyer, Johnson, Crawford, Dascomb, and Rogers, 1960) and Denmark (Godtfredsen and von Magnus, 1959). Paralysis is also a common complication of infection with Coxsackie A7 (Chumakov, Voroshilova, Zhevandrova, Mironova, Itzelis, and Robinson, 1956; Ranzenhofer, Dizon, Lipton, and Steigman, 1958; Grist, 1960). It was believed to be very rare after infections with other enteroviruses. However, during the past few years evidence has been accumulating that paralysis may sometimes be associated with other Coxsackie and Echo viruses (Karzon, Barron, Winkelstein, and Cohen, 1956; Kibrick, Meléndez, and Enders, 1957; Buser, Krech, and Moeschlin, 1957; Hammon, Yohn, Ludwig, Pavia, Sather, and McCloskey, 1958; Steigman, 1958; Lennette *et al.*, 1959; Steigman and Lipton, 1960; Johnson, Shuey, and Buescher, 1960; Meyer *et al.*, 1960; Drouhet, 1960). The paralysis is usually slight in degree and transient, but residual palsies may occur.

In the present series four patients, varying in age from 9 months to 24 years, were seen with features indistinguishable from paralytic poliomyelitis. Types B2 and B5 Coxsackie viruses were isolated and serological studies on two of them showed a rising titre of homologous antibody but no evidence of poliovirus infection. As effective vaccination against poliomyelitis becomes more general, so paralytic cases caused by Coxsackie and Echo viruses can be expected to assume an increasingly large proportion of the total (Lennette *et al.*, 1959).

Despite the prevalence of poliovirus type 1 during 1959, only about 24% of cases diagnosed clinically as non-paralytic poliomyelitis and aseptic meningitis were in fact confirmed as poliovirus infections by virus isolation. In this series only a few cases were examined serologically to exclude poliovirus infection, but similar studies by Lennette *et al.* (1959) and Brown *et al.* (1960) showed that virus isolation techniques were about 90% efficient in diagnosing poliovirus infection. In 1959 almost as many cases of aseptic meningitis were caused by Coxsackie and Echo viruses and mumps as by poliovirus. During 1960 the great majority of the virus-confirmed cases of aseptic meningitis were Coxsackie in origin, poliovirus being less commonly isolated. During both years mumps accounted for about 10% of the cases. The virus of lymphocytic choriomeningitis was not encountered at all. An aetiological diagnosis was established in less than half of all cases of aseptic meningitis during the two-year period, which agrees with the findings of other workers (Lennette *et al.*, 1959; Godtfredsen and von Magnus, 1959; McLean, Walker, and McNaughton, 1960). This contrasts with the high rate of diagnosis in cases of paralytic disease. The percentage efficiency of isolating Coxsackie and Echo viruses is not known, and the more extensive use of serological tests for these viruses might well increase the proportion. However, such tests are at present inconvenient for the routine laboratory.

During 1960 most of the isolations of Coxsackie viruses were from cases of aseptic meningitis. It does not follow, however, that this was the commonest clinical syndrome associated with these viruses in the general population, as only the more severe cases would be admitted to hospital. Coxsackie group B viruses cause also mild febrile illnesses often with upper respiratory symptoms and pleurodynia. The latter illness seems to have been relatively uncommon in the present outbreak, perhaps because type 5 seems to be less

commonly associated with outbreaks of epidemic pleurodynia than other group B viruses (Dalldorf, Melnick, and Curnen, 1959).

With the usual symptomatology of Coxsackie infection virus isolation and rising antibody titre are usually sufficient to establish a causal relationship, but the situation is very different when an illness with unusual features presents. These viruses cause inapparent infections, and, particularly during periods of epidemic incidence, they may be superimposed on unrelated illnesses. This was exemplified by two cases seen during the present study. One was that of a boy with the typical features of mumps followed by aseptic meningitis. Coxsackie type B5 was isolated from his faeces, and during the course of the illness there was a significant rise of both mumps and Coxsackie B5 antibodies. The second case was that of a man of 45 admitted to hospital with severe diarrhoea. Coxsackie B4 was isolated from his faeces, but later his illness was confirmed as ulcerative colitis. Unusual features can be ascribed to Coxsackie infection only if enough virologically proved cases are seen.

Rash is a rare feature of Coxsackie group B infections (Syverton, 1959; Lycke, Hultgårdh, and Redin, 1959), being more commonly recognized in association with Coxsackie group A and Echo viruses. Two cases of Coxsackie B5 aseptic meningitis in the present series had a transient macular rash.

Two further cases from which Coxsackie viruses were isolated were diagnosed as capsulitis or muscle sprain, and no other cause was found for these illnesses. In view of the tendency of the group B viruses to cause acute localized inflammation of muscles it seems likely that these symptoms were also caused by them. However, pain around joints in association with Coxsackie virus infection has not been previously reported.

Eleven cases of encephalitis or meningo-encephalitis were examined during the 1960 Coxsackie outbreak. Of these, two were due to mumps and one to Coxsackie B2. Coxsackie viruses are recognized as important causes of encephalitis in the United States, where they may be responsible for as many as 15–20% of cases (Lennette *et al.*, 1959). The Coxsackie B2 infection in this series was remarkable for the relapsing course of the febrile illness preceding the meningo-encephalitis. It presented great difficulty to clinical diagnosis, especially in differentiating it from tuberculous meningitis, which is important in view of the rigorous treatment required for the latter. Enteroviruses should be considered especially during the season of their prevalence and if other members of the family have experienced febrile upsets at about the same time or shortly before.

Coxsackie infections in young infants and children may be unusually severe and even fatal. Three infants were seen during the present outbreak with evidence of myocarditis and croup. They are considered in detail in a separate communication (Babb *et al.*, 1961). Indeterminate and brief illnesses also occur in small children. These usually take the form of mild febrile disturbances, occasionally with minor respiratory symptoms, and occur in the summer and autumn months. The four cases described above were more severe and presented difficulty in clinical diagnosis. One pair of siblings had convulsions with high fever and drowsiness, lasting 24 hours and three days respectively. No cause other than Coxsackie B4 in the faeces was found. The other pair, also siblings, had severe vomiting and some diarrhoea, and Coxsackie A9 was isolated from both. The latter cases occurred in the winter months and were clinically

diagnosed as winter vomiting disease. I have noticed similar disturbances of the gastro-intestinal tract in small children undergoing poliovirus infection.

Summary

Virological studies are reported on cases of infections of the central nervous system during a two-year period. Poliovirus type 1 was dominant during 1959, whereas Cocksackie viruses types B2 and B5 were more commonly isolated in 1960.

In 1959 62 paralytic cases occurred. From 53 of these, viruses were isolated, all polioviruses. In contrast, in 1960, from 24 paralytic cases 21 virus isolations were made but only 17 (81%) of these were polioviruses; the rest (19%) were Cocksackie virus types B2 and B5.

In aseptic meningitis, virus diagnosis was made in less than half the patients. In 1959 Cocksackie, Echo, and mumps viruses caused almost as many cases as did poliovirus, and during 1960 Cocksackie viruses were responsible for most. During both years mumps caused about 10% of cases.

Cases of unusual symptomatology associated with Cocksackie infection are described. These include not only paralysis but also meningo-encephalitis and rash. In young children there were cases of myocarditis, croup, and a number of indeterminate but severe illnesses difficult to diagnose clinically.

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REFERENCES

- Babb, J. M., Stoneman, M. E. R., and Stern, H. (1961). *Arch. Dis. Childh.* In press.
- Brown, G. C., Lenz, W. R., and Agate, G. H. (1960). *J. Amer. med. Ass.*, **172**, 807.
- Buser, M., Krech, U., and Moeschlin, S. (1957). *Helv. med. Acta*, **24**, 434.
- Chumakov, M. P., Voroshilova, M. K., Zhevandrova, V. I., Mironova, L. L., Itzelis, F. I., and Robinson, I. A. (1956). *Prob. Virol.*, **1**, 16.
- Dalldorf, G. (1951). *J. exp. Med.*, **94**, 65.
- (1952). *J. Mt Sinai Hosp.*, **19**, 396.
- (1955). *Ann. Rev. Microbiol.*, **9**, 277.
- and Albrecht, R. (1955). *Proc. nat. Acad. Sci. (Wash.)*, **41**, 978.
- Melnick, J. L., and Curnen, E. C. (1959). In *Viral and Rickettsial Infections of Man*, 3rd ed., p. 519, edited by T. M. Rivers and F. L. Horsfall, jun. Lippincott, Philadelphia.
- De Lustig, E. S., and Brieux, S. (1957). (Abst.). Tissue Culture Ass. Programme of 8th Annual Meeting, Univ. of Maryland School of Medicine, Baltimore, April 16-17, 1957.
- Dömök, I. (1957). *Acta microbiol. Acad. Sci. hung.*, **4**, 183.
- Drouhet, V. (1960). *Ann. Inst. Pasteur*, **98**, 562.
- Godtfredsen, A., and von Magnus, H. (1959). *Dan. med. Bull.*, **6**, 264.
- Grist, N. R. (1960). *Lancet*, **1**, 1054.
- Hammon, W. McD., Yohn, D. S., Ludwig, E. H., Pavia, R. A., Sather, G. E., and McCloskey, L. W. (1958). *J. Amer. med. Ass.*, **167**, 727.
- Howlett, J. G., Somlo, F., and Kalz, F. (1957). *Canad. med. Ass. J.*, **77**, 5.
- Johnson, R. T., Shuey, H. E., and Buescher, E. L. (1960). *Amer. J. Hyg.*, **71**, 321.
- Karzon, D. T., Barron, A. L., Winkelstein, W., jun., and Cohen, S. (1956). *J. Amer. med. Ass.*, **162**, 1298.
- Kibrick, S., Meléndez, L., and Enders, J. F. (1957). *Ann. N.Y. Acad. Sci.*, **67**, 311.
- Le Bouvier, G. L. (1954). *Nature (Lond.)*, **174**, 649.
- Lennette, E. H., Magoffin, R. L., Schmidt, N. J., and Hollister, A. C., jun. (1959). *J. Amer. med. Ass.*, **171**, 1456.
- Lycke, E., Hultgårdh, A., and Redin, B. (1959). *Lancet*, **1**, 1097.
- McLean, D. M., Walker, S. J., and McNaughton, G. A. (1960). *Canad. med. Ass. J.*, **82**, 661.
- Melnick, J. L., Kaplan, A. S., Zabin, E., Contreras, G., and Larkum, N. W. (1951). *J. exp. Med.*, **94**, 471.
- Meyer, H. M., jun., Johnson, R. T., Crawford, I. P., Dascomb, H. E., and Rogers, N. G. (1960). *Amer. J. Med.*, **29**, 334.
- Ranzenhofer, E. R., Dizon, F. C., Lipton, M. M., and Steigman, A. J. (1958). *New Engl. J. Med.*, **259**, 182.
- Stanley, N. F. (1952). *Proc. Soc. exp. Biol. (N.Y.)*, **81**, 430.
- Steigman, A. J. (1958). *J. Mt Sinai Hosp.*, **25**, 391.
- and Lipton, M. M. (1960). *J. Amer. med. Ass.*, **174**, 178.
- Sulkin, S. E., Wallis, C., and Murphy, T. P., jun. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **84**, 184.
- Syvertson, J. T. (1959). *Amer. J. trop. Med. Hyg.*, **8**, 101.

PERFORATION OF INTERVENTRICULAR SEPTUM AFTER MYOCARDIAL INFARCTION

BY

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Perforation of the interventricular septum occurring after myocardial infarction is being reported more frequently. In a few cases cardiac catheterization has been used for confirmation and to help in deciding the degree of shunt (Muller *et al.*, 1950; Cooley *et al.*, 1957; Gottsegen *et al.*, 1957; Shickman *et al.*, 1959). In at least three patients the defect has been closed surgically (Cooley *et al.*, 1957; Shickman *et al.*, 1959; Romanoff and Cooley, 1960). After septal perforation, although the patient may survive for a few days, the prognosis is generally poor: Sanders *et al.* (1956), in a collective review of 133 cases, found that 50% died within the first week, and that only 13% lived for more than two months. In occasional instances a patient has lived for some years afterwards (Wood and Livezey, 1942; Zucker *et al.*, 1952; Briggs and Holt, 1954). The longest recorded survival time was that of a patient of Schlappi and Landale's (1954), whose acquired ventricular septal defect occurred in 1947, she eventually died from a non-cardiac condition at the age of 83 (Schlappi, 1960, personal communication).

Historical Note

Dr. P. Mere Latham (1846) gave a detailed account of the terminal illness of a patient who can now be diagnosed from the history as having suffered an attack of myocardial infarction. On the fifth day (Friday) after the onset of his patient's cardiac pain there was a recurrence of a more severe attack of pain, and Dr. Latham wrote:

"But on the next day, Friday, I was suddenly called to him. It was six p.m. I found that, about an hour before, the pain had returned with far greater severity than ever. He was deadly pale, and from the centre to the extremities of his body he was cold as marble, and streaming with perspiration; but his pulse was of a good strength, and his heart was contracting regularly and forcibly, and now, for the first time (according to my observation), with a loud systolic murmur, audible in the precordial region, and not in the arteries. I administered a large dose of opium with ether and ammonia. Visiting him again in an hour or two, I