COXSACKIE VIRUSES AND BORNHOLM DISEASE

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In the United States of America and in Canada viruses have been isolated which have been called Cocksackie viruses, from the village of Cocksackie in New York State, where the first known patients resided. The patients from whose stools, blood, or nasal washings the viruses have been obtained have been variously diagnosed as cases of non-paralytic poliomyelitis (Dalldorf and Sickles, 1948; Dalldorf *et al.*, 1949, Jaworski and West, 1949), "summer-grippe" (Melnick *et al.*, 1950), or epidemic myalgia (Curnen *et al.*, 1949). In Canada, Armstrong *et al.* (1950) have isolated the virus from the stools of three children from whom typical poliomyelitis virus was also recovered, from adults in contact with these children, and from a child suffering from a Guillain-Barré syndrome with an ascending Landry type of paralysis.

In some cases both a poliomyelitis and a Cocksackie virus have thus been isolated from the stools of the same patient. The Cocksackie viruses have been isolated not only from stools, blood, and throat swabs, but from sewage and flies.

There seem to be at least five strains of Cocksackie virus present in the United States of America (Howitt and Benefield, 1950): these viruses can be differentiated by a complement-fixation reaction as well as by the neutralizing effect of specific virucidal antibodies.

The Cocksackie viruses are transmissible only to suckling mice and hamsters, which develop paralysis after an incubation period which may be as short as 48 hours. The muscles of infected mice and hamsters exhibit a proliferation of the cells of the sarcolemma sheaths with loss of striation in the muscle fibres: all the voluntary muscles of the body, as well as the diaphragm, show similar changes.

In this country there have been available to us one of the strains isolated in Connecticut by Melnick *et al.* (1949), and three strains known as Dalldorf viruses 1, 2, and 3. We are indebted to Professor Sven Gard, of Stockholm, Dr. F. O. MacCallum, and Dr. J. A. Dudgeon for these viruses.

A Laboratory Infection

During the course of investigations to determine whether there was evidence of interference between the Cocksackie viruses and mouse-adapted strains of poliomyelitis virus a laboratory infection occurred.

E. M. H. had been working with the Cocksackie virus for some three months. On January 3, 1950, towards the evening, she felt pain over the lower left ribs, particularly towards the back. This pain was worse on breathing and became more severe during the night. On the second day of illness the pain was very severe over the lower intercostal spaces on the left side. She found it difficult to breathe. There was no headache, but throughout the day the temperature varied between 99° and 100° F. (37.2° and 37.8° C.). At 2 p.m. it was 99.4° F. (37.4° C.), but at 6.30 p.m. it had fallen to normal. During the third day the patient was afebrile and the severity of the muscular pain gradually decreased. On the fourth day there were no symptoms, but on the fifth day there was a slight but definite return of the muscular symptoms, without, however, a rise in temperature.

On the evening of the second day, when the patient had become afebrile, blood was removed and inoculated intraperitoneally into suckling mice. These mice remained in good health. A complement-fixation test on this serum for immunity to the Cocksackie virus was negative, but a further test on the fourth day after the onset of symptoms gave positive fixation with Cocksackie virus 2, the strain with which most work was being carried out.

A volunteer, whose serum on numerous occasions had given a negative complement-fixation for Cocksackie viruses, was then inoculated intranasally with 0.5 ml. of a 1 in 100 suspension of suckling mice in saline infected with Cocksackie virus 2 and filtered through a Seitz filtrate. This filtrate was active in suckling mice up to a dilution of 10⁻⁷.

No symptoms occurred till 46 hours after the intranasal instillation, when a sudden pain was felt in the intercostal spaces immediately below the point of the right scapula. The pain radiated round the intercostal space: it was more intense on taking a deep breath or laughing, and no position could be assumed in which the pain was completely alleviated. There was no nasal catarrh, and no headache or aching in the limbs apart from the intercostal pain. On the evening of the first day of illness, twelve hours after the onset of pain, the temperature was 99.2° F. (37.3° C.), but on the following morning, after a somewhat uncomfortable night, it was subnormal and the pain was easier. It continued for a further 48 hours and did not recur.

The complement-fixation reaction 24 hours after the onset of symptoms was still negative, but 72 hours after the onset complement-fixing antibodies were detectable in the serum: they have persisted for a period of nine weeks.

In connexion with these infections it is of some interest that two other possible infections have occurred in laboratories in this country to which the Cocksackie virus 2 has been supplied.

In a laboratory in the North of England infected material was handled by a pathologist on February 23 and 24, 1950. On February 28 he felt slightly cold, and severe pain developed round the lower part of the chest on the right side. There was also slight aching in the joints, but the chest pain was the main symptom; it was more severe on breathing or on any sudden movement. The temperature was 99° F. (37.2° C.). The symptoms continued unabated during the next 24 hours and the temperature rose to 104.6° F. (40.3° C.): this rise may have been due to the flaring up of a right maxillary antrum infection, from which the patient had suffered on previous occasions. The patient's blood culture was bacteriologically sterile and no malaria parasites were found in blood films. The symptoms gradually disappeared on March 2 and 3, the temperature being normal on the latter date. On the first day of illness the red cells were 5,500,000 per c.mm.; haemoglobin, 96%: leucocytes 16,100 per c.mm. (polymorphonuclear leucocytes 86%, small lymphocytes 9%, mononuclear cells 4%, eosinophils 1%).

The attack was diagnosed as most probably Bornholm disease, though at the time the patient was not aware of any possible association between Cocksackie virus and the symptoms of Bornholm disease. On the twenty-second day after the onset of symptoms the patient's serum when tested gave a positive complement-fixation reaction with Cocksackie virus 2.

In view of this finding it appeared to be of interest to examine the sera of workers in another laboratory in London where Cocksackie virus 2 had been handled. Of seven sera submitted to the complement-fixation test six were negative for both Cocksackie viruses 1 and 2, but one gave a positive reaction in a dilution of 1 in 20 with Cocksackie virus 2. The donor of the positive serum is unable to recall any illness during the past year which could account for his positive complement-fixation reaction. It is thus possible that he had suffered from a subclinical infection with Cocksackie virus 2, but whether this infection

was contracted during the course of laboratory investigations cannot now be ascertained.

The Complement-fixation Reaction

Complement-fixation tests have been carried out in America by Casals *et al.* (1949) and Howitt and Benefield (1950). The following technique has been employed by us. The antigen is prepared from suckling mice paralysed by an intraperitoneal injection of Cocksackie virus. The skin, viscera, and brain are removed, the carcasses are ground up, and saline is added to form a 5% suspension. The suspension is spun at 3,000 r.p.m. for 30 minutes. Dilutions of the patient's serum in saline are first inactivated for 30 minutes at 56° C. and 0.25 ml. of each dilution is added to 0.25 ml. of antigen, together with 0.25 ml. of complement so diluted as to contain 2 minimum haemolytic doses per volume. The mixtures are shaken and left at 4° C. overnight for from 16 to 18 hours; 0.25 ml. of a haemolytic system containing 2.5% of washed sheep cells and 5 minimum haemolytic doses of amboceptor per volume is added to each tube. The tubes are shaken and placed in the water bath at 37° C. until the tubes containing normal control serum are completely haemolysed.

In carrying out tests antigen prepared from normal non-infected suckling mice is used as well as from the Cocksackie-infected mice. Known positive and known negative sera are always employed together with the sera to be tested. In order to eliminate any personal bias, sera from normal persons and from persons suspected of having had Cocksackie virus have been tested together, the particular sera from suspected infections being unknown to the person carrying out the tests.

In view of the similarity in symptoms between laboratory and experimental infections with Cocksackie virus 2 and those of Bornholm disease it appeared to be of interest to determine whether patients who had been involved in epidemics of Bornholm disease in this country had complement-fixing antibodies to the Cocksackie viruses.

Three small outbreaks of Bornholm disease are known to have occurred in the late autumn of 1949 in (1) Wensleydale, Yorkshire; (2) Richmond and Barnes, Surrey (Hopkins, 1950); and (3) Paddington, London, W.C.1 (Sylvester, 1950, unpublished observations). The results of tests on 18 patients involved in these three outbreaks are shown in

TABLE I.—Complement Fixation by Cocksackie Virus 2 of Sera From Patients with a History of Epidemic Bornholm Disease

Epidemic	Patient	Complement Fixation		
		Cocksackie 2 Antigen	Cocksackie 1 Antigen	Normal Mouse Antigen
Wensleydale . . . (Sept., 1949)	O.M.	1 in 5	0	0
	S.M.	1 in 10	0	0
	W.M.	1 in 20	0	0
Barnes and Richmond (Sept.-Oct., 1949)	J.H.S.H.	1 in 80	0	0
	M.H.	1 in 40	0	0
	A.H.	1 in 40	0	0
	A.B.	1 in 5	0	0
	J.I.	1 in 5	0	0
	O.N.	1 in 10	0	0
	D.W.	1 in 5	0	0
Paddington, London . . (Sept.-Oct., 1949)	M.W.	1 in 5	0	0
	M.S.	1 in 5	0	0
	G.	1 in 20	0	0
	S.	1 in 20	0	0
	H.	1 in 20	0	0
	W.	1 in 20	0	0
	K.	1 in 5	0	0
Aden, 1946 . . .	B.	1 in 5	0	0
	H.	1 in 20	0	0
	D.M.P.	1 in 20	0	0

Table I. It will be seen that all the sera gave positive results in dilutions of 1 in 5 to 1 in 80, the sera having been examined two to six months after the actual attack. One of the sera, that of M.H., was from a boy whose case is

described by Dr. J. H. S. Hopkins in this issue of the *Journal*; he had had meningitic symptoms, which might well have been mistaken for non-paralytic poliomyelitis. D.M.P. was involved in an outbreak in Aden in 1946 (Jamieson and Prinsley, 1947).

In Table II are shown the results of testing sera from persons who had given a history of acute pain in the lower thoracic region resembling that encountered in Bornholm

TABLE II.—Complement Fixation by Cocksackie Virus 2 of Sera From Patients Not Associated with any Epidemic of Bornholm Disease But Having a Suggestive History

Patient	Date of Illness	Location	Complement Fixation		
			Cocksackie 2 Antigen	Cocksackie 1 Antigen	Normal Mouse Antigen
Mrs. J.	March, 1950	Barnes	1 in 5	0	0
E.	June, 1949	"	1 in 10	0	0
J.	Aug., 1949	"	1 in 5	0	0
T.H.D.	Feb., 1949	Liverpool	1 in 10	0	0
D.	Dec., 1949	"	1 in 20	0	0
B.	Sept., 1949	Cumberland	1 in 20	0	0
D.	"	"	1 in 20	0	0
H.	"	"	1 in 10	0	0
B.	Feb., 1950	Manchester	1 in 10	0	0
F.	March, 1950	"	1 in 10	0	0
M.F.	Dec., 1942	Hertfordshire	0	0	0
N.Y.	March, 1950	Northants	1 in 20	0	0
J.Y.	"	"	1 in 20	0	0
E.Y.	No illness	"	0	0	0
D.Y.	"	"	1 in 10	0	0
J.Y.	"	"	1 in 10	0	0

disease: all were positive against Cocksackie virus 2 except one whose attack had occurred eight years previously. Mrs. J.'s first serum was obtained on the fourth day of illness, when complement fixation was positive in a dilution of 1 in 5: a second specimen, obtained on the 15th day of illness, showed positive complement fixation in a dilution of 1 in 10 and a specimen six weeks later 1 in 20. The early occurrence of complement fixation in an apparently sporadic case of Bornholm disease is of interest, since Howitt and Benefield (1950) have noted the presence of complement-fixing antibodies to Cocksackie viruses two, four, four, and five days after the onset of illness, and in an experimental infection in this country complement fixation became positive on the third day after the onset of symptoms. N.Y. and J.Y., two brothers aged 5 and 7, were diagnosed as cases of non-paralytic poliomyelitis, or possibly influenza, but showed no evidence of a rise in titre for influenza viruses. N.Y. had a temperature of 103° F. (39.4° C.) with vomiting and twitching of the facial muscles: J.Y. had a temperature of 99° F. (37.2° C.), with pain in the right hip and twitching of the facial muscles. The sera of the father, mother, and grandfather were negative, but the sera of two other brothers, aged 6 and 13 years, who occupied the same bed as N.Y., were positive although they had had no illness. Cases of true paralytic paralysis had occurred in the same town previously. D.M.P., who had suffered from symptoms suggestive of epidemic myalgia in 1946 when in Aden, was also positive. The complement-fixation reaction given by the serum of T.H.D. is of some interest, since his attack of intercostal pain on the left side was diagnosed and treated as being due to coronary thrombosis.

In addition to the sera reported in Tables I and II six sera from patients diagnosed as suffering from non-paralytic poliomyelitis or lymphocytic meningitis have been examined with negative results; similar negative results have been obtained with the sera of 26 healthy persons giving no history of symptoms suggesting Bornholm disease.

The specificity of the complement-fixation test for Cocksackie viruses has been further examined by testing sera

known to contain antibodies against influenza A and B viruses, or from persons immune to mouse-adapted poliomyelitis viruses, Lansing and M.E.F. 1 strains; Columbia SK virus; meningo-encephalomyelitis; yellow fever; Rift Valley fever; mumps; infective hepatitis; and herpes simplex. Boiling the antigen for five minutes destroys all complement fixation, but heating the antigen for one hour at 56° C. leaves some complement-fixing activity. The filtrate, after passing a suspension of the virus through a gradocol membrane of 31 $\mu\mu$ bore size which retains the virus, still has some complement-fixing action. It thus seems probable that the complement-fixation reaction depends on a soluble-specific substance and not on the virus itself.

Although adult mice do not develop any symptoms suggestive of infection, it has been found that the muscles of adult mice inoculated intraperitoneally three days previously contain sufficient antigen to allow of their being used in the complement-fixation test: on inoculation of a suspension of this adult muscle into suckling mice no infection occurred.

In a small number of cases virus-neutralization tests have been carried out in suckling mice with sera from known Cocksackie virus 2 infections and from cases clinically diagnosed as Bornholm disease: the results parallel those of the complement-fixation test.

Haemagglutination tests using Group O human red cells and the red cells of chickens, pigeons, mice, rats, guinea-pigs, hamsters, and frogs have all been negative. This is in conformity with the negative results obtained by Casals *et al.* (1949).

Discussion

These investigations show that symptoms of myalgia resembling those seen in Bornholm disease (also known as epidemic myalgia, epidemic myositis, epidemic pleurodynia, epidemic pleurisy) occurred in laboratory personnel during investigations with Cocksackie virus 2 and are followed in a few days by the appearance of positive complement-fixing antibodies in the blood.

Cocksackie virus 2 can infect when instilled intranasally, the incubation period being 46 hours: the symptoms resemble those of epidemic myalgia. Here again complement-fixing antibodies and virus-neutralizing antibodies appeared in the serum three days after the onset of symptoms.

Sera from patients involved in three outbreaks diagnosed as Bornholm disease in Barnes and Richmond, Surrey, in West London, and in Yorkshire all fix complement with Cocksackie virus 2 and neutralize this virus, whereas they show no reactions with Cocksackie virus 1 or 3 or with normal mouse antigen. Complement-fixing antigen was present in the serum of a sporadic case of epidemic myalgia as early as the fourth day of infection.

One patient with symptoms of abdominal pain and lymphocytic meningitis has shown complement-fixing antibodies with Cocksackie virus 2. Other patients not associated with an epidemic of Bornholm disease have shown complement-fixing antibodies after a history of sudden myalgia in the chest. These patients have been variously diagnosed as sporadic cases of Bornholm disease, coronary thrombosis, non-paralytic poliomyelitis, and intercostal neuralgia, and have been scattered throughout England from Cumberland to Surrey. The sera of two brothers who had had no illness gave a positive complement fixation: they had occupied the same bed as their brother, who was positive and had been thought to have non-paralytic poliomyelitis.

The activity of the Cocksackie virus antigen is destroyed by boiling for five minutes; it is reduced by heating at

56° C. for one hour, but is not entirely destroyed. So far as complement fixation goes, Cocksackie 2 and the Melnick strain examined by us appear to be closely related. It is not improbable that strains of Cocksackie virus 2 are present in this country, and their presence in cases of non-paralytic poliomyelitis requires further study. The occurrence of meningitic symptoms in epidemics of Bornholm disease has been not infrequently reported (McConnell, 1945; Gsell, 1949).

While this communication was in the press a virus closely resembling Cocksackie virus 2 was isolated from the blood, stools, and nasal washings of a patient who had developed typical symptoms of Bornholm disease 52 hours previously: complement-fixing antibodies for Cocksackie virus 2 were present in his blood at this period. In addition complement-fixing antibodies against Cocksackie virus 1 have been found in the blood of adults recovered from Bornholm disease in Hertfordshire, and in the blood of an adult resident in Versailles, France: two children from Northamptonshire, diagnosed as possibly non-paralytic poliomyelitis, have also fixed complement with Cocksackie virus 1 but not Cocksackie virus 2.

Conclusions

Cocksackie virus 2 can infect the adult intranasally, producing symptoms resembling those of Bornholm disease.

Cocksackie virus 2 has been isolated from the nasal washings and blood of an adult with Bornholm disease.

Complement-fixing antibodies and virus-neutralizing antibodies develop within three days of the onset of symptoms after experimental infection.

Patients from epidemics of Bornholm disease in England and Aden show complement-fixing and virus-neutralizing antibodies against Cocksackie viruses 1 or 2 but not against Cocksackie virus 3. Such antibodies are present by the third day of infection and may show an increase in titre.

Some cases of Bornholm disease with lymphocytic meningitis have complement-fixing antibodies against Cocksackie virus 2.

Sporadic cases with pain in the chest, with various diagnoses including non-paralytic poliomyelitis and coronary thrombosis, have antibodies against Cocksackie viruses 1 or 2.

The evidence suggests that Cocksackie viruses 1 and 2 are widely distributed in Great Britain and that some epidemics of Bornholm disease in this country are associated with infection by Cocksackie virus 1 or 2 or very closely allied viruses.

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ABACTERIAL FORM OF ENDOCARDITIS WITH NECROSIS OF THE EARS

BY

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The case here reported, in which symmetrical necrosis affected the ears of a patient with the clinical features of subacute bacterial endocarditis, will be found of interest. Repeatedly negative blood cultures, failure to respond to penicillin, myocardial infarction, and death in uraemia were other unusual features.

Case Report

A labourer aged 30 was admitted to hospital on February 27, 1947. He had had rheumatic fever at the age of 6 and schizophrenia at 25. In August, 1946, he had been admitted to St. Mary Abbots Hospital complaining of headaches, rigors, and pain and bleeding of both pinnae. He had an irregular fever and showed signs of mitral stenosis and aortic incompetence. Seven blood cultures were sterile. The haemoglobin was 83%; white blood cells varied from 5,000 to 8,000 per c.mm. (neutrophils 31–60%, lymphocytes 29–40%, monocytes 5–27%). The urine contained red blood cells and occasional hyaline and granular casts. He was treated with penicillin, 80,000 units three-hourly for seven weeks—a total of 31,000,000 units. Some lowering of the temperature occurred, but there was little improvement in the general condition, and he discharged himself from hospital on October 30, 1946.

On admission to the Central Middlesex Hospital he complained of malaise, anorexia, and rigors. Ten days previously he had developed a sudden pain in his left arm which spread to the left of the sternum and lasted two days.

Examination revealed clubbing of nails, healthy teeth, a small haemorrhage in the right fundus, and regular pulse. Blood pressure 150/60. The heart was not enlarged. There were signs of mitral stenosis and aortic incompetence. The liver and spleen were enlarged to three fingerbreadths below the costal margin, and the spleen was tender. On the left pinna a tender blue area with incipient necrosis was present.

Investigations.—Eight blood cultures taken between February 28 and April 3 were sterile. Aerobic and anaerobic cultures were maintained for 14 and in some cases 21 days. The urine contained albumin and many red blood cells. Blood urea rose from 66 to 274 mg. per 100 ml. Plasma proteins: albumin 3 g., globulin and fibrinogen 4.5 g. per 100 ml. Takata-Ara, + + +. Thymol turbidity test, 15 units. Serum colloidal gold reaction, + + + +. Haemoglobin fell from 56% to 40%, and the white blood cells varied from 5,000 to 16,000 per c.mm. The sedimentation rate (Westergren) rose from 98 to 124 mm. per hour. The Wassermann reaction was negative. The urea clearance was 12% of normal. Serial electrocardiograms showed the characteristic appearances of a recent anterior cardiac infarction (Fig. 1). Biopsy from the left pinna on March 27 showed many greatly dilated capillaries, some of which contained small projections of endothelium-covered fibrinoid material. Full pathological details have been published by Pagel (1949).

A diagnosis of subacute infective endocarditis was made. The cardiac infarction was considered embolic in origin. The patient had an irregular fever up to 101° F. (38.3° C.) for the first six weeks. After the eight sterile blood cultures penicillin was started, 200,000 units being given every three hours for six weeks—a total of 70,400,000 units. Although his temperature became lower his general condition deteriorated. On April 13 he awoke with pain in the right pinna, which was found to be reddened and swollen, with mottled blue areas, and a few days later necrosis appeared. Meanwhile separation of the necrotic portion of the left pinna occurred (Fig. 2). He died in uraemia on June 10, 1947.

Post-mortem Examination.—The chief abnormal findings were as follows.

Heart:—Weight, 460 g. (normal 300 g.). The aortic valve was bicuspid and showed a number of yellowish-red vegetations up to 0.5 cm. long, the largest of which lay close to the orifice of the left coronary artery. There was marked narrowing of the anterior descending branch of the left coronary artery 3 cm. from its origin. A healed infarct was present at the apex of the left ventricle. **Kidneys:**—right, 230 g.; left, 240 g. (normal 125–170 g.); flea-bitten appearance; scar of old infarct on left. **Liver:**—1,930 g. (normal 1,400–1,600 g.); well-marked nutmeg appearance. **Spleen:**—450 g. (normal 150–200 g.). **Brain:**—recent infarct in right parietal cortex and small cyst in right occipital lobe.

Histology.—**Aortic valve:**—Extensive red and white thrombotic vegetations. No bacteria seen in Gram preparation. **Myocardium:**—Fresh changes consisting of small focal areas of interstitial infiltration with polymorphs and mononuclear cells, presumably embolic in origin. Old changes presumed to be rheumatic, consisting of scars and small areas of perivascular fibrosis and calcification surrounded by a few multinucleated giant cells and lymphocytes. **Kidney:**—Most of the glomeruli showed patchy and chronic changes. Many of the tufts were partially replaced by connective tissue. Proliferative and endothelial changes were slight, and no crescents were seen. Interstitial fibrosis and patchy tubular atrophy were present. It

FIG. 1.—Electrocardiogram taken on March 4, 1947, showing changes of recent anterior cardiac infarction.

FIG. 2.—Necrosis of pinnae, with impending separation of the left pinna, April 28, 1947.