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Case Reports

COXSACKIE PERICARDITIS

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SINCE Dalldorf and Sickles isolated the Coxsackie viruses in 1947, the pleomorphic nature of the disease processes produced by these organisms has become increasingly obvious. For some time it has been recognized that meningitis, meningoencephalitis, epidemic pleurodynia, herpangina and orchitis may occur, singly or in combination, in the course of such infections. More recently the involvement of the myocardium has been demonstrated,[1-3] and the complete and beautifully documented studies of the group from South Africa[4-7] are particularly convincing. Idiopathic benign pericarditis (I.B.P.) has for some time been suspected of being due to a virus infection, partly because no other cause was obvious and partly because the condition had not infrequently been noted in association with diseases long recognized as of virus etiology. Weinstein[8] described a case of acute benign pericarditis in which a significant rise of antibody titre to Coxsackie virus group B type 5 was demonstrated. Fletcher and Brennan[9] published a similar case in which antibodies to Coxsackie B4 were found. Movitt *et al.*[10] made further progress by recovering Coxsackie virus from the stools of two adult patients with pericarditis, and by demonstrating in each a rise in the appropriate antibody. McLean and his colleagues[11] have recently added to the evidence by publishing four cases of benign pericarditis in children (together with nine of epidemic pleurodynia), all of whom had Coxsackie B5 in the fæces and showed a rise in antibody titre.

The case for abandoning the term "idiopathic" for such cases is thus very strong, and we would perhaps be justified in using the descriptive phrase acute viral pericarditis for the majority of cases. We wish to add to the record a further adult case of proven Coxsackie infection in which an unusual variety of signs and symptoms was manifested, including those of pericarditis.

R.A., a white male medical laboratory assistant, aged 31, noticed symptoms first on October 12, 1958, when he complained of malaise, headache and slight sore throat. Like many persons within the medical milieu he decided to treat himself, but symptoms persisted and an increase in the severity of the headache prompted him to report sick on October 16. He was found to be febrile (101° F.) with a pulse rate of 100 and a normal respiratory rate. The only physical signs detected were a mild injection of the fauces and slight neck stiffness. A chest radiograph was negative. The hæmoglobin level was 13.5 g. %, white blood cell count 9000 with normal differential count,

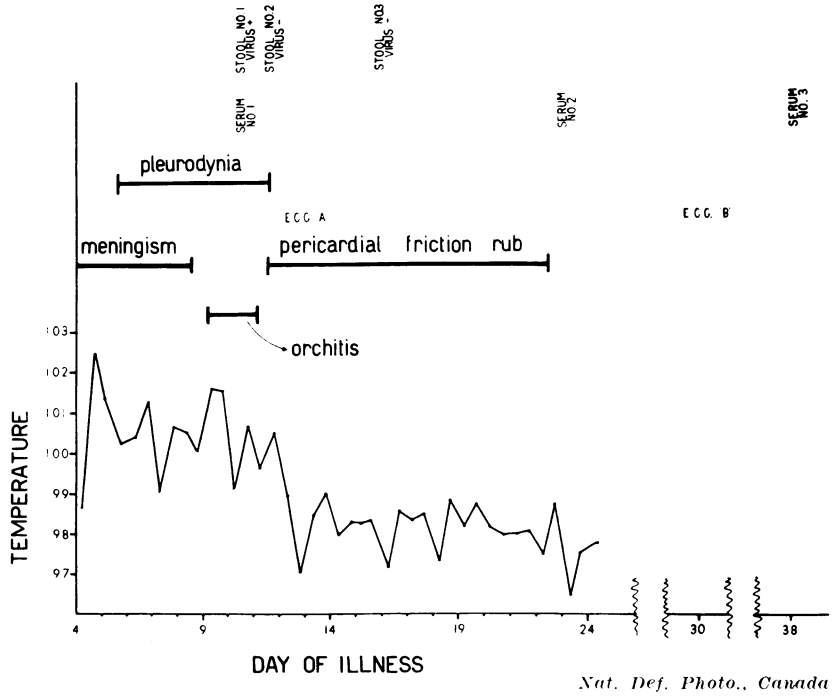

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Fig. 1.

erythrocyte sedimentation rate 23. The urine showed a specific gravity of 1017, no albumin or sugar and, microscopically, scattered pus cells, a few epithelial cells and an occasional unidentified cylindroid. He did not appear very sick but was admitted for observation. On October 17, he still complained of headache, vertigo on rising to the sitting position, stiffness of the neck and pain in the left side of the chest and left shoulder aggravated by breathing. The fauces remained injected, but at no time were any lesions resembling herpangina seen. Lumbar puncture was not performed because the patient was not very willing and because it was felt that the confirmatory evidence it would have offered did not justify insistence on the procedure, particularly as the neck stiffness and headache were subsiding and a diagnosis of bacterial meningitis was most unlikely. Aureomycin 250 mg. 8-hourly was administered but with no obvious effect. He remained febrile with a swinging temperature (Fig. 1) for several days. The white cell count remained in the vicinity of 10,000, and nothing pathogenic was cultured from the fauces. He continued to complain of pain in the left chest on breathing, though the radiograph

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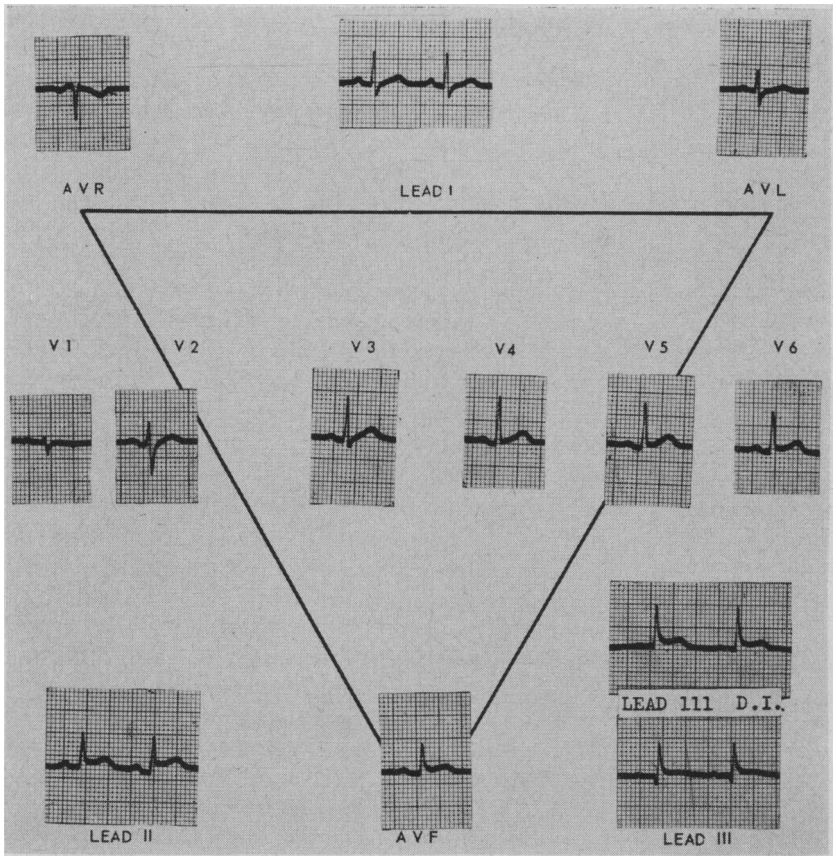

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Fig. 2.—Electrocardiogram A taken on October 24, 1958.

remained negative. On October 21, he developed pain in both testicles, and these were tender to palpation though not obviously swollen or inflamed. This lasted about 48 hours. By October 23, the febrile phase was subsiding but he remained rather weak and was noted to be dyspnœic on minor exertion. On this day, for the first time a very loud friction rub became audible over the whole of the precordium but maximal along the left sternal edge. The heart was not enlarged clinically though the radiograph showed a minor degree of enlargement. The heart sounds were loud and apparently normal, though auscultation was somewhat hampered by the loud friction rub. There was no venous congestion and no evidence of paradoxical behaviour of either venous or arterial pulse on inspiration.

On October 24, an electrocardiogram (Fig. 2) demonstrated S-T elevations in leads II, III, IIID.I., AVF, V5 and V6, which, though minimal, were consistent with pericarditis.

The patient was kept at strict bed rest and his remaining symptoms rapidly subsided. The friction rub remained audible till November 3, and during this time no increase in heart size or evidence of pericardial effusion was demonstrated. After this, he was allowed to take exercise gradually but he became tired and dyspnœic very easily and his pulse rate remained elevated even at rest. While these phenomena are known sequels of many severe virus infections, we felt it at least possible that the myocardium was involved and thought it wise for him to progress very cautiously towards full activity. On November 10, an electrocardiogram (Fig. 3) showed frank T wave inversions in leads II, III, IIID.I. and AVF and all precordial leads. Since then tracings have shown changes towards normality. On December 11, he was asymptomatic and clinically normal and was returned to duty.

Isolation of Virus

Stools were collected on the 6th, 7th and 12th days of illness. A 1:10 emulsion of each was prepared in balanced salt solution, penicillin and streptomycin were added, and 1-ml. quantities were used for infection of monkey kidney cell tissue cultures. After six days' incubation at 37° C. cytopathogenic effect was observed in the culture infected from the 6th-day specimen. Further tissue cultures were infected, a total of six serial passages being made. It was also found possible to pass the virus from monkey kidney cell cultures to human amnion tissue cultures.

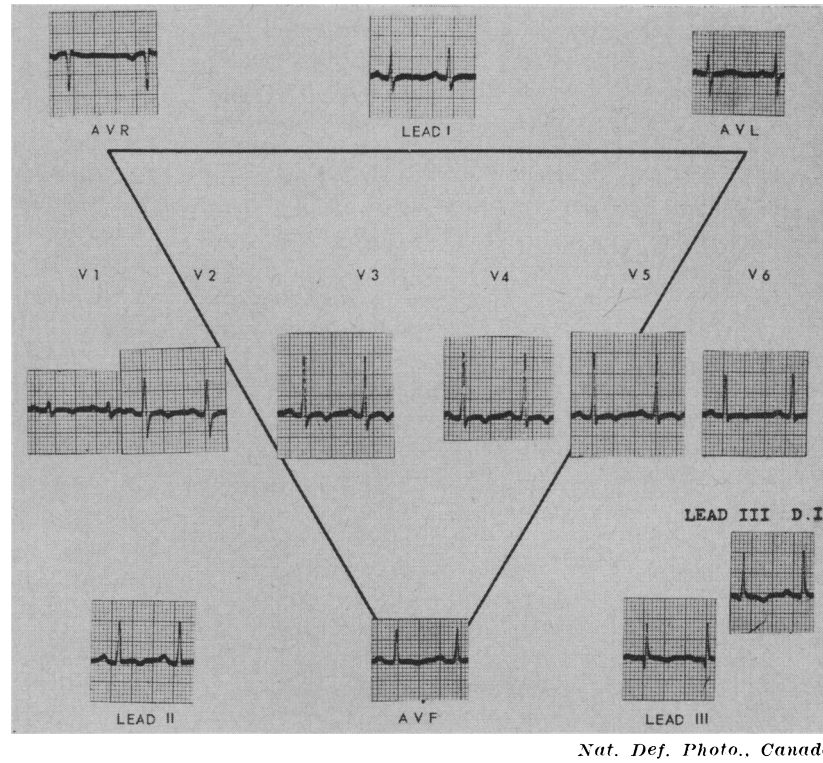

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Fig. 3.—Electrocardiogram B taken on November 10, 1958.

Canad. M. A. J.
May 1, 1959, vol. 80

Typing of Virus

The CPE producing agent grown from stool on tissue culture was subjected to neutralization tests against type-specific antisera. The range employed included Coxsackie A9, B1, B2, B3, B4 and B5 antisera. Specific neutralization of the unkown virus by B5 antiserum was demonstrated. Duplicate typing tests conducted at the School of Hygiene, University of Toronto, confirmed the presence of Coxsackie B5 virus.

Three litters of randomized 24-hour-old mice were inoculated intracerebrally (0.02 ml.) and three litters intraperitoneally (0.05 ml.), using each of the three 10% stool suspensions. These animals were observed for a period of 14 days, during which time they remained healthy. Two litters of mice of a similar age were inoculated both intracerebrally and intraperitoneally with monkey kidney tissue culture fluid. From the litter inoculated intraperitoneally, two mice showed paralysis of the forelegs after six days. Histological sections of skeletal muscle showed no lesions. Changes characteristic of Coxsackie B virus infection were observed in the interscapular hibernating gland fat pads. These included peripheral congestion, necrosis, infiltration with inflammatory cells and intercellular granularity. Sections of brain showed no marked changes.

Virus Neutralization Studies

Serum No. 1 from the patient, collected on the 11th day of illness, neutralized Coxsackie B5 virus in a dilution of 1:128. Serum No. 2, collected on the 23rd day of illness, showed a rise in titre to 1:1024. Serum No. 3 (38th day) neutralized in a dilution of 1:512.

DISCUSSION

This case thus fulfils the criteria laid down by Kilbourne[12] for a proven and specific virus etiology. There can be little doubt that the Coxsackie B5 virus was responsible for this miscellany of symptoms and signs. The variety of symptoms was of course invaluable in diagnosis, and in fact the case had been labelled a Coxsackie infection clinically by one of us (M.J.L.) before the pericarditis became evident. Had the chest pain and evidence of pericarditis occurred alone in a man of this age, a confident diagnosis of I.B.P. would probably have been made. The symptoms were never such as to suggest myocardial infarction — the condition regarded by Reid *et al.*[13] as most likely to be confused with this form of pericarditis.

The term "benign" has been widely accepted in relation to this condition, and it is generally assumed that the outcome of I.B.P. is almost invariably good if pericardial tamponade is watched for and promptly treated. In the 23 cases of Reid *et al.*[13] there was only one fatality—from tamponade —and apparently there was a return to normality in all the others. In a review of the literature Price *et al.*[14] could find only four cases with a fatal outcome, and of these three patients died in tamponade. These authors described a further fatal case in which a large pericardial effusion was found post mortem. Not all of these cases were published with full pathological reports, but when the myocardium was reported on it was said to be normal except for a polymorphonuclear leukocyte infiltration of the subepicardial myocardium. It is believed that the typical electrocardiographic changes, which may persist for several months, are due to this superficial myocardial involvement.[15] At times the ECG changes are gross and it may be difficult to reconcile them with only a minor subepicardial lesion. However, Kisch[16] has demonstrated that superficial lesions of the myocardium have a disproportionately great effect on the electrocardiogram, and that these lesions may be structurally so minor as to be difficult to detect microscopically.

The article by Simenhoff and Uys[5] and that of Javett *et al.*[3] describe the pathological findings in infants dying of Coxsackie myocarditis, and make it clear that in such patients the myocardial involvement is severe and widespread. It seems that the neonate is particularly liable to such infections, and there is some evidence that older children may be involved.[17] It has been suggested that neonates are particularly prone to develop Coxsackie myocarditis because of their high circulating levels of corticoids. Adult mice are normally resistant to Coxsackie B virus infections, but Kilbourne *et al.*[18] were able to produce extensive myocardial damage by giving cortisone to the inoculated animals. These authors speculated on the possible dangers of converting benign viral disease in adult patients to a much more serious infection by the untimely use of corticoids.

At present there seems to be no positive evidence for the occurrence of widespread or serious Coxsackie myocarditis in adult patients, and the available pathological data, though scanty, certainly do not indicate any lasting myocardial damage. The case of Fletcher and Brennan,[9] however, showed numerous premature contractions persisting over a period of two months, and they wondered whether this was due to myocardial involvement. It is certainly hard to understand how an exclusively pericardial or epicardial process could produce this effect. Myocarditis not infrequently complicates poliomyelitis, and we think that it would be dangerous to assume that myocarditis never occurs in the acute phase of adult Coxsackie infections. We have been impressed by the dyspnœa and persistently high pulse rates shown by patients in the convalescent phase of I.B.P. when tamponade could not be demonstrated and the hæmodynamics of the heart were apparently unimpaired. In any case, it would seem prudent to withhold corticoids from all patients suspected of suffering from a Coxsackie infection and certainly from all acute cases of pericarditis unless a diagnosis of rheumatic infection is unequivocal. It would also seem wise to insist on a prolonged convalescence from I.B.P. so far as this is feasible.

We wish to express our indebtedness to Professor C. E. van Rooyen for his interest and for the enthusiasm with which he placed his experience and specialized facilities at our disposal.

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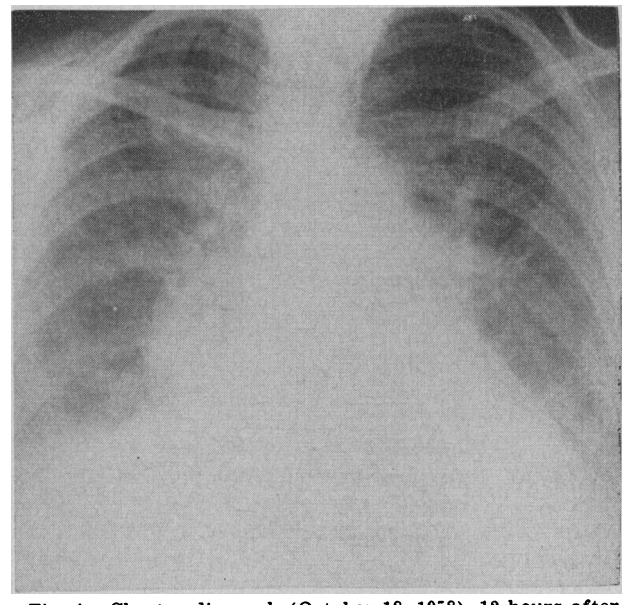

Fig. 1.—Chest radiograph (October 18, 1958), 12 hours after admission, indicates generalized cardiac enlargement and pulmonary congestion. There is a density in the right lower lung field consistent with a pneumonic consolidation.

CONGESTIVE HEART FAILURE CAUSED BY SENSITIVITY TO DIPHENYLHYDANTOIN (DILANTIN SODIUM)

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FOR THE PAST quarter-century, it has been known that a non-antigenic chemical may unite with blood protein to form a specifically reactive antibody.[1] Drugs in common usage, such as sulfonamides, iodides, Dilantin sodium (diphenylhydantoin), phenobarbital, arsenicals, and thiourea, may incite hypersensitivity reactions indistinguishable from serum sickness, periarteritis nodosa, and hypersensitivity angiitis. Because they are so commonly used, consideration of their role in the etiology of unusual vascular and systemic syndromes[2] is important. The lesions may vary from subacute to acute, with involvement of the intimate vasculature of the skin and any or all of the viscera. Myocarditis, pneumonitis, nephritis, or diffuse dermatitis may predominate. The medical condition is frequently alarming and may be fatal.

The following report describes an acute hypersensitivity reaction related to the use of Dilantin sodium. The salient clinical feature was rapidly developing congestive heart failure.

A.T., a 49-year-old white woman, hotel manager, was first admitted to the service of Dr. J. Mayer at the New Mount Sinai Hospital, Toronto, on September 12, 1958, and discharged after investigation on September 19, 1958. During the preceding four months, she had suffered three attacks of grand mal convulsions without aura. In each case, the attacks had occurred about one week before menstruation. Her previous health had been normal. She was a robust-appearing, moderately overweight woman. Her height was 63 in., weight 167 lb., blood pressure 120/80 mm. Hg, pulse rate 80. There were no abnormal physical findings. The heart was of normal size with regular rhythm and no murmurs. The urine was normal, grossly and microscopically. The hæmoglobin value was 15.5 g., W.B.C. 7400, blood smear normal. The blood Wassermann reaction was negative. Lumbar puncture revealed a spinal fluid pressure of 150 mm. H_2O, one white and one red cell, protein 17 mg. %, colloidal gold 012210000; fasting blood sugar 108 mg. %, N.P.N. 33 mg. %. An air encephalogram was normal. A diagnosis of idiopathic grand mal epilepsy was made, after which the patient was sent home on a maintenance dose of 0.1 g. diphenylhydantoin (Dilantin sodium) 3 times a day.

She remained symptom-free until October 15, 1958. On this date, fever and rash appeared. Despite this she continued on medication. Three days later her physician examined her at home and noted a well-marked maculopapular rash involving the face, trunk and extremities. The oral temperature was 103° F. There were no other findings. The diphenylhydantoin was discontinued. On the next day, I was asked to see her by her physician because of a serious deterioration in her clinical state. On examination she was orthopnœic and cyanosed. The oral temperature was 102° F., respiration rate 35, pulse rate 130, blood pressure 110/70 mm. Hg. Auricular fibrillation was present. There were coarse and fine rales throughout both lung fields, particularly in the right base. The neck veins were distended. The liver was two fingers'-breadths below the costal margin, enlarged and tender. The rash was still brilliant. The patient was admitted to hospital immediately. On arrival, oxygen therapy was instituted. Twenty-five units of ACTH and 1 mg. of digoxin were administered intramuscularly; 8 mg. of triamcinolone was given orally, with repeated doses of 4 mg. 4-hourly. The next morning she was more comfortable. Auricular fibrillation persisted with an apical rate of 110. The temperature had fallen to 100°

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