Medical Memoranda

Fatal Coxsackie B₃ Myocarditis in a Newborn Infant

[WITH SPECIAL PLATE]

Coxsackie B infection can give rise in young infants to a widespread systemic infection involving particularly heart muscle and nervous tissue. The present case came to light during routine post-mortem virological studies from the British Perinatal Mortality Survey in 1958. It is presented because of the absence of previous reports of neonatal Coxsackie B infection in Britain, though Coxsackie B myocarditis has recently been recorded in older infants (Babb *et al.*, 1961) and in a young adult (Glajchen, 1961).

CASE REPORT

A female weighing 3,185 g. was born on April 5, 1958, at home in South London after an uneventful full-time pregnancy and normal labour. On the ninth day the infant suddenly developed a cyanotic attack followed by laboured respirations. On admission to hospital in poor condition two hours later the lips and extremities were cyanosed, respirations were grunting, and the liver was palpable. A full anterior fontanelle led to examination of the cerebrospinal fluid; this was clear and colourless, with 16 polymorphs and 13 lymphocytes per c.mm.; protein 35 mg., sugar 22 mg., chlorides 680 mg. per 100 ml.; no organisms present on smear or culture. Treatment in oxygen with tetracycline by mouth was unavailing and death occurred six hours later.

From the fifth to the ninth day post partum the mother had been feverish and unwell, which the family doctor attributed to influenza. The father had suffered just previously from a similar transient illness.

FINDINGS AT NECROPSY

Lungs.—All lobes were partially atelectatic and congested, with occasional bilateral subpleural petechial haemorrhages. Histologically, the bronchioles and respiratory ducts appeared normal; the majority of the alveoli were expanded and showed no changes, but a few contained mononuclear cells and an occasional polymorph. A few small foci of alveolar, septal, and subpleural haemorrhage of asphyxial type were present.

Heart.—Weight 25 g. Valves, endocardium, and septa normal; ductus patent. About 4 ml. of clear yellow fluid present in the pericardium. Microscopically, there were focal collections of histiocytes and mononuclear cells with an occasional polymorph lying in the myocardial connective tissue. These collections of cells varied in size from a single discrete focus of 20 to 50 cells to a more diffuse lesion of several hundred such cells lying between unaffected muscle fibres (Special Plate, Fig. 1). There was no collagenous necrosis and no tendency to paravascular distribution of these lesions. A scanty but more diffuse infiltration of similar cells was present in the epicardium and endocardium.

The lesion, though predominantly a myocarditis, could be more properly regarded as a pancarditis.

Abdominal Cavity.—About 20 ml. of clear yellow fluid was present.

Liver.—Weight 140 g.; appearance normal. Microscopically, small areas of cell necrosis of irregular size, shape, and distribution were present. In these areas the liver cells at the centre were lysed. The immediately adjacent sinusoids were dilated and engorged with blood; there was a relatively slight cellular reaction with some lymphocytes and a few polymorphs (Special Plate, Fig. 2).

Other Organs.—Brain (446 g.), spleen (10 g.), kidneys (41 g.), thymus (4 g.), stomach, thyroid, trachea, and oesophagus were normal macroscopically and microscopically. Meninges, gall-bladder, bile-ducts, lymph-nodes, intestines, pancreas, urogenital tract, uterus, adnexae, and pituitary gland were also grossly normal.

Bacteriology.—Lung, peritoneum, and pericardium showed no pathogenic organisms in smears or culture.

VIRAL STUDIES

Heart, lung, and brain tissues were received in a single container on solid carbon dioxide, and 10% suspensions of each tissue were made in 5% normal rabbit serum in saline. The supernatants, after centrifugation and checks for bacterial sterility, were inoculated into HeLa, primary human amnion, and primary monkey kidney cell cultures maintained at 37° C. Suckling mice under 24 hours old were inoculated either intraperitoneally (inoculum 0.03 ml.) and/or intracerebrally (inoculum 0.01 ml.).

The Table indicates the time sequence observed in the production of cytopathic effect in the inoculated tubes. Tissue-culture fluid (fourth passage) obtained from monkey kidney tubes inoculated with heart suspension was employed to type the virus isolated, and this was determined as a Coxsackie B₃ virus.

Paralysis developed within six to seven days in all the suckling mice inoculated with the original suspension of heart muscle and in 40% of the mice inoculated with tissue-culture fluid from monkey kidney cultures. Lung suspension produced paralysis in eight to nine days in 55% of the suckling mice inoculated. Sera from surviving mice inoculated with heart and lung suspensions were shown to contain neutralizing antibodies to Coxsackie B₃ virus. Only 20% of suckling mice (2 out of 10) appeared sick eight days after inoculation with brain suspension, and no virus was isolated on passage. The sera of the surviving mice of the first litter were found to contain neutralizing antibodies to Coxsackie B₃ virus.

The results obtained from cell culture and inoculation of suckling mice show that the virus occurred predominantly in the heart. It is not possible to say whether the finding of virus in lung and brain resulted from post-mortem contamination.

DISCUSSION

Typical features consisted in the sudden onset of a severe illness in the second week of life and a history of a recent undiagnosed febrile illness in adult contacts, in this case both parents being involved. The rapid fatal outcome in the infant precluded diagnosis in life. At necropsy myocarditis was present histologically, and this was the first clue that the illness had been due to

Table Showing Isolation of Virus in Tissue Culture

Host System	Heart (Days)			Lung (Days)					Brain (Days)			
	3	4	20	3	6	8	11	20	3	4	5	20
HeLa	3/3 + + + +			3/3 +					3/3 -			
Primary monkey kidney		3/3 + +			1/3 +	1/3 + +	2/3 -			1/3 +	1/3 + +	
„ human amnion	*		3/3 -					3/3 -			2/3 +	3/3 -

Numerator = No. of tubes affected; denominator = No. of tubes inoculated.

* A primary monkey kidney 4th-passage tissue-culture fluid produced CPE in 1/3 tubes of human-amnion-cell cultures after "blind" passage.
+ + + + = Complete degeneration; + + + = degeneration of 75% of cell culture; + + = degeneration of 50% of cell culture; + = degeneration of 25% of cell culture; - = no degeneration of cell culture.

the Cocksackie B₃ virus which was later isolated from heart muscle. Pleocytosis in the cerebrospinal fluid suggested cerebral involvement; however, the presence of virus-neutralizing antibody in surviving newborn suckling mice after injection with brain tissue was not conclusive, as this finding could have been due to post-mortem contamination. Liver necrosis, also confirmed histologically, has been reported previously (Kibrick and Benirschke, 1958).

Babb *et al.* (1961) pointed out that sporadic cases due to Cocksackie B₃, B₄, or B₅ have been reported in the past from the U.S.A., Hawaii, Transvaal, and Australia, while outbreaks have been reported as occurring in maternity homes or nurseries in Johannesburg, Capetown, Southern Rhodesia, Amsterdam, Czechoslovakia, and Hungary. Identical virological studies were carried out in the same laboratory without isolation of Cocksackie or other enterovirus on 12 other cases of perinatal death from Southern England and on 10 from the Manchester region during the spring of 1958 in the same survey. Elsewhere strains of Cocksackie B₃ virus were isolated in small numbers from both healthy children and patients in the South of England at this time (Gamble, 1961). No virological studies were carried out on the parents in our case, but proved Cocksackie B infection has been reported frequently to be associated with infantile myocarditis, the adult form usually being "summer gripe," non-bacterial meningitis, or Bornholm disease (epidemic pleurodynia). Clinical manifestations were limited to acute cardiac failure in the present case, but there may be lethargy, pallor, collapse, respiratory distress, tachycardia, arrhythmias, or electrocardiographic changes of myocardial damage in T waves or S-T segment. Treatment is non-specific, but a proportion of cases appear to recover. Digitalis has been reported as beneficial (Suckling and Vogelpoel, 1958). Corticosteroids, though reported by some to be of benefit (Javett *et al.*, 1956; Hosier and Newton, 1958), have produced gross myocardial necrosis in adult mice infected with Cocksackie B₃ virus (Kilbourne *et al.*, 1956), and thus should be used only with great caution. As regards prophylaxis, at times when enterovirus infections are prevalent in the community newborn infants should not be concentrated in nurseries, and if at home should be kept away from adults.

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Reviews

TUMOUR-INDUCING VIRUSES

Oncogenic Viruses. By Ludwik Gross, M.D. (Pp. 393+xi; illustrated. 80s.) Oxford, London, New York, Paris: Pergamon Press, 1961.

The appeal of a book devoted to viruses that induce tumours or are associated with tumours in a variety of species is largely confined to experts in this fascinating domain of cancer research. So far as the reviewer can tell from a careful study of its close-on-400 pages it succeeds in its praiseworthy programme. Experts on virus research will no doubt demur over details and may even violently combat Dr. Gross's hypotheses. In any case, things move so rapidly nowadays with undertakings that are carried out with vigour and enthusiasm that personal opinions are often out of date by the time they are published. Granted such reservations, there is still so much in Dr. Gross's book for the general reader that a notice such as this one will at least have some value by indicating the scope of the volume.

First and foremost there is a masterly introduction to the methods employed and to ways of thinking about tumours transmitted by transplantation or by filtrates, and how such information leads us to suspect the presence of a virus in a tumour. We then pass on to a group of fairly simple fibromas, papillomas, and related neoplasms, including human warts and papillomas that are infectious and transmissible. Graduating by way of the Lucké frog-kidney carcinoma and the contagious venereal dog sarcoma, with a pause to take breath on the more familiar level of the Rous chicken sarcoma—rather an old friend, this one, since many of us have grown up with it—we tackle the chicken leukoses. These prepare us for the great adventure of the book, the leukaemia problem. Quite properly Dr. Gross gets us ready for the severe demands that we are about to face through an admirable chapter on mouse mammary carcinoma. Now we become aware of the importance of inbred strains of mice and their impact on experimental cancer research and, incidentally, are thrilled by the story of the Bittner filterable agent and its natural transmission through the milk of nursing mice.

And so we reach two of the most exciting moments in the chronology of cancer investigation: the recovery of leukaemia-producing agents from mice inoculated, when newborn, with cell-free extracts from other tumours, and the astonishing polyoma story. The four chapters which unfold this bit of contemporary history are not easy reading for the uninitiated since so much of it is still coming in from the laboratory front line. However, Dr. Gross proves an excellent guide through this observational maze. Finally he tells us much about the search for oncogenic viruses in human beings and suggests a working hypothesis for the aetiology of cancer. Here the general reader will revel in the clarity of the account of cancer and leukaemia in families and in successive generations in man, and in the lucid discussion of the experimental transmission of human tumours.

To sum up, this is a book written by a master in the field of viruses and cancer research, who possesses a strong historical sense, writes clearly and critically, and

F. O. STEPHENS: SYNDROME OF INTESTINAL PSEUDO-OBSTRUCTION

FIG. 1.—(A) Erect and (B) supine abdominal radiographs from Case 2 on admission, showing dilated small and large bowel with fluid levels, but gas can be seen extending all the way down to the rectum.

FIG. 2.—(A) Erect and (B) supine abdominal radiographs from Case 3 on admission, showing dilated large bowel with fluid levels. The appearance is suggestive of caecal volvulus.

FIG. 3.—(A) Erect and (B) supine abdominal radiographs from Case 4 on admission, showing grossly dilated large bowel with fluid levels.

N. BUTLER *ET AL.*: NEONATAL COXSACKIE B MYOCARDITIS

FIG. 1.—Myocardium, showing an inflammatory focus consisting of histiocytes and lymphocytes with an occasional polymorph. (H. and E. $\times 188$.)

FIG. 2.—Liver. A relatively pale area in the top right-hand quadrant is a focus of necrosis of hepatic cells. (H. and E. $\times 188$.)