particular any evidence of progressive respiratory embarrassment, must arouse suspicion of hydrothorax or haemothorax. An early danger signal that can easily be overlooked is the failure of the patient to respond to fluids and drugs administered via the catheter (cases 1 and 2). The time factor is not constant—damage to the vein wall may occur some hours or days after insertion of the catheter (cases 3 and 4).

On examination of the patient the physical signs of respiratory distress and fluid in the pleural cavity are obvious. Immediate investigations—depending on the urgency of the situation—commence with a plain chest *x*-ray film. This may be of value in that not only will the size and situation of the effusion be seen, but also the site of the catheter. This can be seen only if the catheter is radio-opaque (Doering *et al.*, 1967), and it appears that unfortunately even now not all types of catheter are radio-opaque. For final proof of the extravascular site of the catheter, injection of a marker dye, if there is immediate access to its drainage channels—for example, a thoracotomy drain or radio-opaque medium (which can be seen on *x*-ray film)—may be made into the catheter.

It may be of value to know whether the pleural fluid is clear fluid (from the infusion) or blood (from the damaged vein) and to this end immediate tapping of the effusion with a syringe and No. 1 needle can be performed. If clear fluid only is obtained formal chest aspiration may be adequate to relieve the situation, though the possibility of thoracotomy and control of bleeding from the perforation must be borne in mind, and may be deemed to be the preferable initial treatment.

Finally, it cannot be overemphasized that most of the complications that arise from the use of central venous pressure catheters are due directly or indirectly to poor technique. Sepsis can be almost eradicated if strict precautions are taken, and the problem of hydrothorax stems from incorrect or unsuccessful attempts at venous catheterization. Blood should always be aspirated freely before a catheter is assumed to be in place—both at the time of insertion and later during use for injection of drugs. The catheter should also be fully stabilized after insertion by taping it firmly to the skin.

Common-sense precautions such as these may prevent a valuable technique from producing a life-threatening disaster.

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References

Adar, R., and Mozes, M. (1970). *Journal of the American Medical Association*, **214**, 372.
Adar, R., and Mozes, M. (1971). *British Medical Journal*, **3**, 746.
Arnold, S., Feather, R. S., and Gibbs, E. (1973). *British Medical Journal*, **1**, 211.
Aulebacher, C. E. (1970). *Journal of the American Medical Association*, **214**, 372.
Bolasny, B. L., Shepard, G. H., and Scott, H. W. (1970). *Surgery, Gynecology and Obstetrics*, **130**, 342.
Colvin, M. P., Blogg, C. E., Savage, T. M., Jarvis, J. D., and Strunin, L. (1972). *Lancet*, **2**, 317.
Darrell, J. H., and Garrod, L. P. (1969). *British Medical Journal*, **2**, 481.
Doering, R. B., Stemmer, E. A., and Connolly, J. E. (1967). *American Journal of Surgery*, **114**, 259.
English, I. C. W., Frew, R. M., Piggott, J. P., and Zaki, M. (1969). *Anaesthesia*, **24**, 521.
Henzel, J. H., and DeWeese, M. S. (1971). *American Journal of Surgery*, **121**, 600.
Jernigan, W. R., Gardner, W. C., Mahr, M. M., and Milburn, J. L. (1970). *Surgery, Gynecology and Obstetrics*, **130**, 520.
Latimer, R. D. (1971). *British Journal of Hospital Medicine*, **5**, 369.
Mahaffey, J. E., and Witherspoon, S. M. (1966). *Anesthesiology*, **27**, 198.
Northfield, T. C., and Smith, T. (1970). *Lancet*, **2**, 584.
Thomas, C. S., Carter, J. W., and Lowder, S. C. (1969). *Archives of Surgery*, **98**, 217.
Walker, M. M., and Saunders, R. C. (1969). *Anaesthesia*, **24**, 453.
Wellman, K. F., Reinhard, A., and Salazar, E. P. (1968). *Circulation*, **37**, 350.
Wilmore, D. W., and Dudrick, S. J. (1969). *Archives of Surgery*, **98**, 256.

PRELIMINARY COMMUNICATIONS

Diabetes in Mice after Coxsackie B_4 Virus Infection

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Summary

The intraperitoneal inoculation of CD_1 mice with Coxsackie virus B_4 resulted in the raising of blood sugar levels to diabetic values 12 days after the administration of the virus. Serum insulin remained inappropriately low. Light microscopy changes in the islets of Langerhans showed mononuclear cell infiltration of the islets and marked degranulation of the β cells. The acinar tissue appeared to be little changed. It is concluded that Coxsackie B_4 virus may cause a diabetic state compatible with islet cell damage.

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Introduction

In recent years much interest has been aroused by reports of virus-induced diabetes in animals. Diabetes complicating foot-and-mouth disease in cattle was reported in Italy (Barboni and Manocchio, 1962) and Craighead and McLane (1968) gave conclusive evidence that a heart-adapted strain of encephalomyocarditis virus (E.M.C.) causes diabetes in certain strains of mice. Burch *et al.* (1971) reported islet and acinar cell damage in mice after Coxsackie B_4 and B_1 virus infections, though blood sugar and insulin levels were not recorded.

We now present data showing the development of diabetes in mice after Coxsackie B_4 virus inoculation.

Methods

Male CD_1 mice (Charles River Mouse Farms, England) were 8-9 weeks old at the time of inoculation. They were given free access to food and water at all times.

The Coxsackie B_4 virus was a prototype strain propagated in tissue culture fluid and titrated in suckling mice less than 24 hours old. Each test animal was inoculated intraperitoneally with 0·2 ml of virus suspension containing 100 LD_{50}. Control animals were inoculated with 0·2 ml of sterile tissue culture maintenance medium.

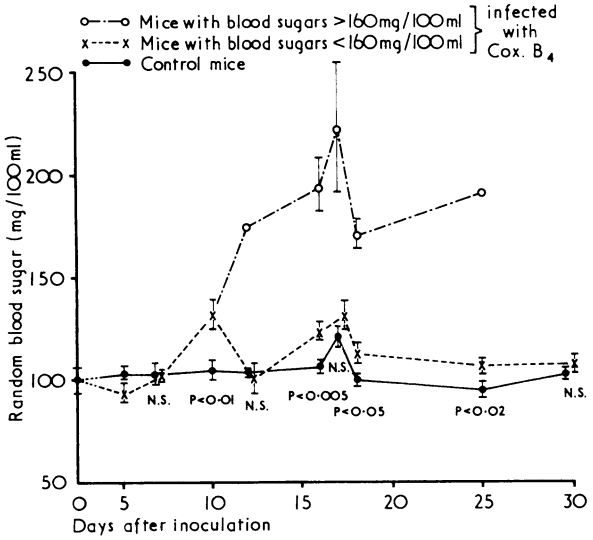
Blood sugar estimations were made using tail vein blood and using the GOD-Perid method (Boehringer-Mannheim G.m.b.H.).

Serum insulin was measured by a modification of the radioimmunoassay described by Hales and Randle (1963).

For histology the pancreas was fixed immediately after death of the animal in buffered 10% formalin in saline and stained using Gomori's aldehydefuchsin, haematoxylin and eosin, and rhodinile blue (MacConaill and Gurr, 1964) to show α and β islet cells and the presence of mononuclear cells.

Results

Changes in random blood sugar values at various times after incubation are shown in the graph. Values given show means and, where numbers are appropriate, S.E. of means. For the controls and those mice with blood sugars less than 160 mg/100 ml each point on the graph represents a group of eight mice, whereas for mice with blood sugars greater than 160 mg/100 ml each point shown, with S.E., represents six mice.



Changes in random blood sugar values at various times after incubation. Values are means ± S.E. of mean. N.S. = Not significant.

Five days after inoculation there was a small fall in the blood sugar levels in the infected mice compared with controls. Thereafter the control and infected animals had similar blood sugars until day 10 when the treated animals showed significantly higher blood sugars. By day 12 some mice were obviously diabetic (random blood sugars > 160 mg/100 ml) and this was most noticeable by 17-21 days after inoculation. Glucose tolerance tests on mice showing random blood sugars of more than 160 mg/100 ml showed typically diabetic curves.

Serum insulin levels in the infected mice were consistently higher than controls throughout the course of the experiment. However, the serum insulin levels in the diabetic mice, though higher than the controls, were inappropriately low for the raised blood sugar levels present. (In two mice with blood sugars of 400 mg/100 ml at 17 days the serum insulins were only 43 and 47 μU/ml compared with 20 μU/ml in control animals.) These findings suggested that the β cells may have had higher basal rates of insulin release due to cell damage but that they were unable to release an adequate amount of insulin to control a rise in blood sugar.

Light microscopy of pancreases from hyperglycaemic mice showed evidence of pronounced β cell degranulation in many islets though some islets remained intact and appeared normally granulated. Though there were areas of acinar cell degeneration these were not numerous and much of the acinar tissue appeared completely unaffected. A mononuclear cell infiltration was seen around many, but not all, damaged islets and there was evidence of the invasion of some islets by mononuclear cells.

Discussion

Evidence is accumulating that certain picornaviruses can cause islet cell damage and diabetes in animals, but these viruses have been types that do not commonly infect man. So far as we are aware this is the first time that a picornavirus which is a common human pathogen has been shown to be capable of causing islet cell damage associated with diabetic changes. The course of the infection described appears to involve an initial lowering of the blood sugar and slight raising of serum insulin levels at about five days—that is, about the time that the virus is present in large amounts in the pancreas—followed by either a return of blood sugar to normal values or to diabetic values in some animals.

Unlike the E.M.C. virus of Craighead and McLane (1968), we have not found it necessary to adapt our stock Coxsackie B_4 virus in any way, but, as in their experiments, it is necessary to select a suitable strain of mouse. By using Coxsackie B_3 virus and E.M.C. viruses we have found very variable results depending on both the adaption of the virus and the strain of mouse used (see table).

Our results indicate that the changes observed in mice after Coxsackie B_4 virus infection may be a suitable model for the development of diabetes after a viral infection, and show that the changes are restricted to only a proportion of mice of identical strain, age, and sex infected with the same virus. In addition, the delay between inoculation and onset of diabetic changes may well indicate a mechanism involving some general response to viral infection rather than a direct local attack on islet cell by the virus alone.

Since there have been suggestions that Coxsackie B_4 virus is sometimes associated with diabetes in man (Gamble *et al.*, 1969; Gamble and Taylor, 1969) it is of interest that this virus can cause a typical acute diabetic state in experimental animals. It is, however, too early to be sure what relevance these studies have to most cases of human diabetes.

Results found on Adaptation of Virus and Strain of Mouse

Strain of Mouse (All Male)	Cox.B_3P_6	Cox.B_3P_8	Cox.B_3P_{14}	Cox.B_3M_{12}	E.M.C. unadapted
Porton (8-9 weeks)	Pancreatitis. Islets normal. Blood sugars normal	Pancreatitis. Islets normal. Blood sugars normal	—	—	—
DBA (8-9 weeks)	—	Severe pancreatitis. Normal islets. Blood sugars subnormal	—	Slight pancreatitis. Normal islets. Blood sugars normal	Severe pancreatitis. Normal islets. Blood sugars subnormal
CD (8-9 weeks)	Pancreatitis. Normal islets. Blood sugars normal	Pancreatitis rare. Generally normal islets but some islets degranulated. Blood sugars raised in animals with damaged islets	Pancreatitis. Normal islets. Blood sugars subnormal	Slight pancreatitis. Normal islets. Blood sugars normal	Severe pancreatitis. Normal islets. Blood sugars subnormal

P6, P8, P14 = Number of passages through pancreases of suckling mice. M12 = Number of passages through hearts of suckling mice. E.M.C. = Encephalomyocarditis virus.

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References

Barboni, E., and Manocchio, J. (1962). *Archivo Veterinario Italiano*, 13, 447.
Burch, G. E., Ching-Ya Tsui, Harb, J. B., and Colcolough, H. L. (1971). *Archives of Internal Medicine*, 128, 40.
Burch, G. E., Tsui, C. Y., and Harb, J. M. (1971). *Experimentia*, 28, 310.
Craighead, J. E., and McLane, M. F. (1968). *Science*, 162, 913.
Gamble, D. R., Kinsley, M. L., FitzGerald, M. G., Bolton, R., and Taylor, K. W. (1969). *British Medical Journal*, 3, 627.
Gamble, D. R., and Taylor, K. W. (1969). *British Medical Journal*, 3, 631.
Hales, C. N., and Randle, P. J. (1963). *Biochemical Journal*, 88, 137.
MacConaill, M. A., and Gurr, E. (1964). *Irish Journal of Medical Science*, 6, 243.

MEDICAL MEMORANDA

Pulseless Disease Presenting with Isolated Abducens Nerve Palsy and Recurrent Cutaneous Angiitis

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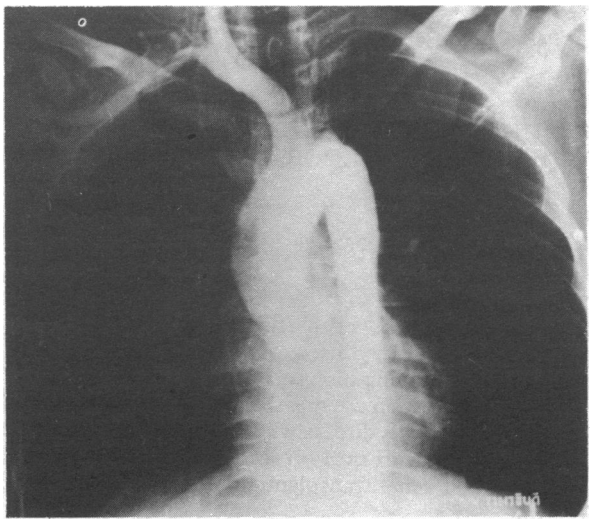
The clinical features of pulseless disease are the result of inadequate blood supply to certain organs such as the brain, eyes, and upper limbs due to narrowing or occlusion of the main branches of the aorta. The outstanding presenting symptoms are visual disturbances, ranging from photopsia and blurring to blindness, and syncopal attacks, often with convulsions. We report here a case of pulseless disease which presented with isolated abducens nerve palsy. We believe this is the first report of an isolated cranial nerve palsy associated with this disease. Cutaneous lesions similar to those described by Takezawa *et al.* (1966) as tuberculide-like eruptions and by Grimaldi (1970) as cutaneous micro-angiitis were also present.

Case Report

A 20-year-old man was admitted to hospital because of headache and double vision. He had been well until two years before, when he started having intermittent throbbing headache, which usually began in the right frontal region but soon radiated to the occiput and on some occasions also to the left side. The headache was worse on waking in the morning and sometimes it awakened him during the night. There was no associated nausea, vomiting, or fever. The attacks had been almost daily but with occasional interludes of up to three months. Three months before admission he had had pain in and around the right orbit and a month later had developed double vision. Five years previously he had had intermittent skin eruptions, which he described as "black dots," over the upper parts of both arms and over the back, and for the past two years these had persisted.

On admission the patient's blood pressure was 120/70 mm Hg in the right arm and 100/90 in the left. It was unobtainable in either leg. There was hyperpigmentation of the dorsal aspect of both thighs and papulonecrotic eruptions measuring 3-5 mm in diameter over the chest wall, the back, and all the extremities. The white cell count was 14,100/mm^3 with 67% neutrophils, 23% lymphocytes, and 10% monocytes. Serial erythrocyte sedimentation rates over a two-week period were 35, 37, 96, and 79 mm in the first hour (Westergren). Serum protein electrophoresis showed the albumin to be 2·6 g/100 ml and globulin 4·16 g/100 ml, the globulin fractions being alpha$_1$ 2·4%, alpha$_2$ 10·8%, beta 18·7%, and gamma 19·5% All other findings, including examination of the cerebrospinal fluid, were within the normal range. A purified protein derivative tuberculin skin test was negative at 1:1,000 but positive at 1:100.

A radioactive brain scan was normal. Electroencephalography showed background activity of moderate amplitude with waves of alpha frequency seen posteriorly. There was some higher-amplitude, irregular, slow activity from the right hemisphere, more prominently from the posterior temporal region. *X*-ray examination of the chest, skull, and cervical spine and an intravenous pyelogram showed nothing abnormal. A retrograde transfemoral aortogram (see fig.) showed complete obstruction of the left common carotid artery at its origin with good collateral circulation via the thyrocervical trunk and intercostal arteries. The left subclavian artery was not seen and there was no evidence of subclavian steal syndrome. An abdominal aortogram showed partial obstruction and doubling of the right renal artery. The right internal carotid artery did not fill on right brachial angiography. The right vertebral artery and the posterior communicating artery were enlarged, feeding blood to both cerebral hemispheres through collateral circulation.



Retrograde transfemoral aortogram showing complete obstruction of left common carotid artery at its origin and no evidence of left subclavian artery.

Biopsy of tissue from a papulonecrotic lesion on the back showed focal spongiosis of the epidermis leading to intraepidermal vesicle formation. Patchy cellular infiltration was present in the vicinity of blood vessels and adnexal structures of the dermis. The cellular infiltrate consisted of lymphocytes with a few neutrophils in some areas. Giant cells were also present. There was narrowing of the capillary lumen from oedema of the endothelial cells. The findings were consistent with papulonecrotic tuberculide and pityriasis lichenoides et varioliformis acuta of Mucha and Habermann, both of which represented two forms of vasculitis.

The patient's throbbing headache persisted in hospital, but his stay was otherwise uneventful and he was discharged after 25 days.

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