

## Development of incisional hernia

	Year 1	Year 3	Year 5
No of patients followed up	564	482	431
No of new hernias	28	14	6

factor for which there was a significant difference between patients who had developed a hernia by one year (75% wound infection) and those who developed one subsequently (38% wound infection) ( $p < 0.05$ ).

Factors that showed no significant difference between the two groups were sex, obesity, malnutrition, malignant disease, coexisting medical conditions, type of incision, postoperative chest infection, and suture materials used. Preliminary data from the follow up after seven years showed that a new hernia had developed in a further four patients out of the 376 patients studied.

## Comment

We are unaware of any previous long term follow up of a cohort of patients undergoing abdominal surgery to determine the incidence of incisional hernia. Previous studies have usually reported the incidence of hernia at periods up to one year postoperatively, and this has been regarded as the definitive incidence. Clearly this is a serious underestimate, since the incidence may be expected to double after one year.

The use of a single observer minimised the possibility of observer error as a cause of these new findings. Three possible explanations suggest themselves. A hernia too small to be detected clinically may have been present at the time of first examination and subsequently enlarged to become obvious. Subclinical hernias may certainly be present in obese patients, but if this is the explanation it would still represent a new finding in relation to previous, shorter term studies. Secondly, mature fibrous tissue may slowly stretch and weaken with time. A third possibility is that scar tissue may be a more dynamic tissue than has previously been recognised, so that metabolic stresses on the patient might result in a catabolic effect on the dynamic equilibrium of continuing resorption and laying down of new collagen. This latter suggestion is purely speculative, since we do not have any evidence to support or refute it. Whatever the explanation, it seems that wound infection is less important in the hernias that develop late; wound infection has been well recognised in the past as the most important factor in hernias of early onset.

Studies seeking to ascertain the incidence of incisional hernia should continue for at least five years; even then, however, the figure will be an approximation because hernias may still develop in a very few cases.

<sup>1</sup> Kline A, Hughes LE, Campbell H, Williams A, Zlosnick J, Leach KG. Dextran 70 in the prophylaxis of thromboembolic disease after surgery: a clinically orientated randomized double-blind trial. *Br Med J* 1975; ii:109-12.

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## Calcium antagonist withdrawal syndrome: objective demonstration with frequency-modulated ambulatory ST-segment monitoring

Calcium ion antagonists have excited considerable interest in the treatment of all forms of angina pectoris.<sup>1-3</sup> Once these drugs become widely available situations may arise where patients stop taking medication intentionally or otherwise, and it is important that the effects of abrupt withdrawal and its safety are clearly established. We have documented the effects of withdrawal of calcium ion antagonists

by ambulatory monitoring of the ST segment with a frequency-modulated tape recorder<sup>4</sup> and noted a clear deterioration in the signs and symptoms of myocardial ischaemia in five patients. These cases are reported to document this phenomenon, which has great practical importance.

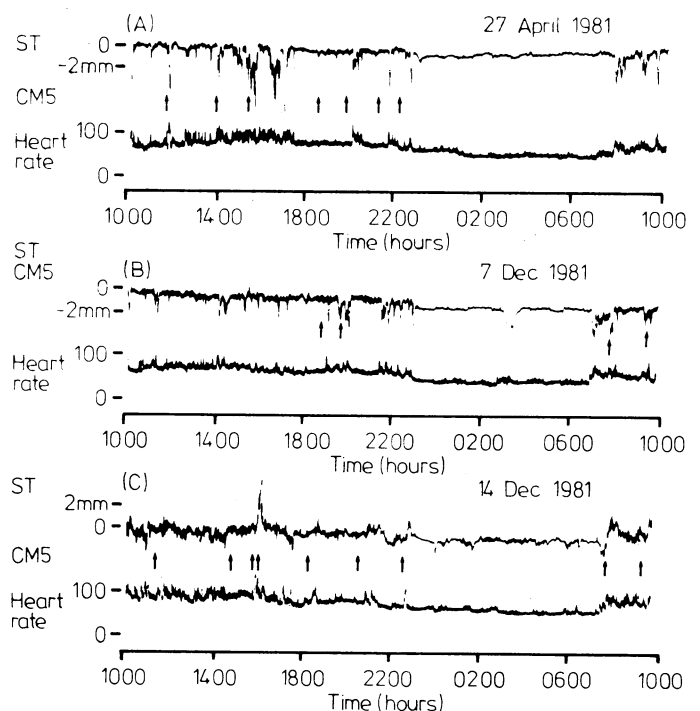
## Case reports

**Case 1**—A 47 year old woman presented with a history of repeated episodes of precordial pain occurring at rest and often associated with syncope. Twenty-four-hour ambulatory monitoring showed elevation of the ST segment and ventricular arrhythmias associated with symptoms. Coronary arteriography showed normal coronary arteries with spontaneous spasm of the left anterior descending artery. She was prescribed verapamil 80 mg six-hourly and became asymptomatic. During a routine follow-up ambulatory monitoring session she overslept and omitted to take her morning dose of verapamil. She was awakened by angina, which was controlled by verapamil. The ambulatory tape showed a pronounced alteration in the electrocardiogram with tall peaked T waves, peaked P waves, and ST-segment elevation before, during, and after the episode of pain. She continued to be asymptomatic after this episode taking verapamil.

**Case 2**—A 71 year old man had chronic stable angina of three years' duration associated with triple-vessel obstructive coronary artery disease. Verapamil 120 mg thrice daily improved his exercise tolerance to 10 minutes and reduced the frequency of his anginal episodes. Repeated clinical and exercise evaluation confirmed the stability of his symptoms and exercise tolerance. After six months of treatment his supply of verapamil tablets became exhausted and he thought that he could manage without them. After 24 hours he began to have severe angina at rest which did not respond satisfactorily to sublingual nitrates. Ambulatory tape recording showed multiple episodes of deep ST-segment depression, some of which were associated with anginal attacks. There was no change in the heart rate during these periods of pain and ST depression. Verapamil was restarted and he became asymptomatic within 48 hours.

**Case 3**—A 52 year old man had chronic stable angina of three years' duration due to confirmed obstructive coronary artery disease. A 24-hour ambulatory ST-segment tape during placebo showed 33 episodes of pronounced ST depression with a maximum depth of 4.2 mm; he had seven episodes of angina during this period. Diltiazem was prescribed and produced considerable improvement. After six months, the drug was withdrawn over a period of four days as a part of a controlled trial, and he was re-evaluated after stopping all treatment. He complained of recurrence of angina, and a 24-hour ambulatory ST-segment trend chart showed seven episodes of ST elevation in addition to numerous bouts of ST depression; the frequency of angina increased to nine attacks in 24 hours (figure). Diltiazem was restarted and the ST-segment elevation abolished.

Similar findings were documented in two further patients when diltiazem was withdrawn in the same controlled trial.



Case 3. Ambulatory electrocardiograms (lead CM5) and heart rate tracings during treatment with placebo (A) and diltiazem 120 mg thrice daily for 24 weeks (B) and after withdrawal of diltiazem (C). Episodes of angina indicated by arrows. Calibration marker shows 2 mm changes.

**Comment**

Identifying withdrawal phenomena is important when treating chronic disease such as angina. The patient or his physician may stop the antianginal medication for various reasons without realising the potential problems which may arise. If withdrawal syndromes exist, it is essential that they should be clearly recognised and the potential complications anticipated.

Our observations indicate that withdrawal of calcium antagonists may be associated with severe angina, a phenomenon which has also been described with beta-adrenergic-blocking drugs.<sup>5</sup> The mechanism of this withdrawal syndrome is unknown. Movement of calcium ions across the membranes of smooth-muscle cells of the coronary arteries is known to maintain arterial tone and the ability of the arteries to contract spasmodically. If the intracellular calcium ion values were depleted by chronic treatment with drugs blocking calcium entry, an artificial situation in which a normal extracellular calcium value and a low intra-cellular calcium value may be created, producing an increased "calcium gradient" across the cell wall. When the drugs are stopped there could be an increased movement of calcium ions into the cells producing a considerably increased tendency for the coronary arteries to go into spasm. Other contributing and provocative mechanisms may possibly play a part in this phenomenon.

The true incidence of this phenomenon is difficult to assess. These cases were encountered during routine ambulatory monitoring of 143 patients on calcium antagonist trials yielding an incidence of about 3.5%, similar to a reported 5% incidence of withdrawal symptoms during beta-blocker treatment.

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Requests for reprints should be sent to Dr E B Raftery.

- Schamroth L. The philosophy of calcium ion antagonists. In: Zanchetti A, Krikler DM, eds. *Calcium antagonism in cardiovascular therapy. Experience with verapamil*. Amsterdam: Excerpta Medica, 1981:5-9.
- Bala Subramanian V, Paramasivan R, Lahiri A, Raftery EB. Verapamil in chronic stable angina: a controlled study with computerised treadmill exercise. *Lancet* 1980;i:841-4.
- Bala Subramanian V, Bowles M, Lahiri A, Davies AB, Raftery EB. Long-term antianginal action of verapamil assessed with quantitated serial treadmill stress testing. *Am J Cardiol* 1981;48:529-35.
- Bala Subramanian V, Lahiri A, Raftery EB, Green H, Stott FD. Ambulatory ST segment monitoring. Problems, pitfalls, solutions and clinical application. *Br Heart J* 1980;44:419-25.
- Shand DG, Wood AJJ. Propranolol withdrawal syndrome—why? *Circulation* 1978;58:202-3.

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## Simultaneous primary infections with Epstein-Barr virus and measles virus in fatal acute encephalitis

We present the first published report of a case of fatal encephalitis in which infection took place simultaneously with Epstein-Barr virus and measles virus. It is also the first report of IgM antibodies to Epstein-Barr virus being found in the cerebrospinal fluid.

**Case report**

A previously healthy 11 year old boy was admitted to a general hospital with headache and transient fever. Four days after admission he developed nausea, vomiting, double vision, tremor, and vertigo and he had hyperactive

reflexes and severe ataxia. The next day he had amnesia and convulsions, temperature had risen to 40°C, and he went into a coma. Findings of contrasted computed tomography were normal. Cerebrospinal fluid pressure, cell count, and protein value (0.60 g/l) were within normal ranges. The boy was subsequently transferred to Rigshospitalet, Copenhagen, in coma, with universal hypotonia, Babinski's sign on the right side, and absent corneal reflexes. He also had bilateral tonsillitis with trismus. Blood count showed a white cell count of  $7.3 \times 10^9/l$  (61% lymphocytes, of which many were atypical cells, and 38% neutrophils). Repeated lumbar puncture yielded clear cerebrospinal fluid containing  $14 \times 10^6/l$  white cells (78% mononuclear), no red cells, a glucose concentration of 5.3 mmol/l (95 mg/100 ml) (plasma glucose concentration being 7.4 mmol/l (133 mg/100 ml)), and a protein concentration of 3.88 g/l. A limulus test for the presence of endotoxin in the cerebrospinal fluid gave negative results. A virus infection with encephalitis was suspected, and the boy was treated with acycloguanosine. Clinical impression of increasing intracranial pressure prompted treatment with mannitol, frusemide, and corticosteroids, but there was no improvement. The boy died eight days after appearance of the initial symptoms. Necropsy showed diffuse oedema of the brain but no macroscopic meningeal reaction. Light microscopic examination of brain biopsy specimens showed extensive perivascular lymphocyte infiltrations.

This patient was exposed to two primary infections simultaneously, one due to Epstein-Barr virus and the other to measles virus. The diagnosis of infectious mononucleosis was supported by the clinical picture and double-checked serologically with the findings of IgM antibodies specific for Epstein-Barr virus in serum (titre 1/320) and cerebrospinal fluid (1/2), a heterophil antibody response, a high serum Epstein-Barr viral capsid antigen (IgG) titre (1/640), and a serum antibody response to the diffuse component of early antigen to Epstein-Barr virus (1/10). The primary measles infection was shown by a positive result to a measles-specific IgM test (enzyme-linked immunosorbent assay)<sup>1</sup> in serum (0.55) and cerebrospinal fluid (0.16), controlled for unspecific rheumatic factor. Furthermore, high titres were found on complement fixation test (1/128) and measles-specific IgG test (enzyme-linked immunosorbent assay, 1.90). Antibody values were also obtained in cerebrospinal fluid (complement fixation test result 1/4, enzyme-linked immunosorbent assay 1.61). The cut-off value in both enzyme-linked immunosorbent assays was 0.15.<sup>1</sup> No clinical evidence of measles was observed. Serum antibodies to adenovirus, influenza virus A + B, respiratory syncytial virus, and parainfluenza virus were all within normal ranges, no antibodies being found for cytomegalovirus. No herpes simplex virus was found in cerebrospinal fluid. At necropsy, brain and lung tissue were cultured for herpes simplex virus and cytomegalovirus, but not for measles virus or Epstein-Barr virus. All cultures were negative. The ratio of cerebrospinal fluid albumin to serum albumin was high ( $68.2 \times 10^{-3}$ , normal range:  $2.7-8.3 \times 10^{-3}$ ), but the IgG index derived from the ratio fell within normal range.

**Comment**

Primary lethal infection with two viruses at the same time has been reported in a few cases<sup>2-4</sup>; this is the first report of simultaneous lethal infection with Epstein-Barr virus and measles virus in a patient with encephalitis. Infection with Epstein-Barr virus seldom causes severe central nervous system symptoms but the cell-mediated immune functions are suppressed in the early stages of infectious mononucleosis. Infection with measles virus also causes immune suppression, and measles encephalitis may be severe and have lasting sequelae. Considering that measles infection in children with congenital T-cell deficiency has a poor prognosis, we suggest that the grave central nervous system symptoms in our patient were secondary to the combined immunosuppressive effects of the two virus infections. Our finding of antibodies in the cerebrospinal fluid could be due exclusively to passive diffusion, as judged from the relatively high albumin ratio. However, the quantitative/qualitative value of blood-brain barrier tests are still under debate.<sup>5</sup> Furthermore, earlier reports have confirmed the possibility of local production of antibodies in cerebrospinal fluid, and the possible passive transfer of albumin and IgG does not guarantee transfer of the much larger IgM molecule.

We conclude that in cases of unusually severe virus encephalitis it might be worth while to check for infection with more than one agent, and if possible to look for changes in the various T-cell subpopulations.

Requests for reprints should be addressed to Mads Melbye.

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<sup>1</sup> Pedersen IR, Antonsdottir A, Evald R, Mordhorst CH. Detection of measles IgM antibodies by enzyme-linked immunosorbent assay (ELISA). *Acta Pathol Microbiol Scand [B]* 1982;90:153-60.

<sup>2</sup> Bland JD, Lilleyman JS. Fatal pneumonia associated with two viruses in a child with lymphoblastic leukaemia. *Br Med J* 1982;284:82.

<sup>3</sup> Smith RH. Fatal adenovirus infection with misleading positive serology for infectious mononucleosis. *Lancet* 1979;i:299-300.