temporally associated with serial reduction of the lamotrigine dose. Valproate, acutely and chronically, alters the half-life of lamotrigine by as much as 100%.[3] This case highlights this interaction and the potential for serious toxicity. Clearly the dosage of lamotrigine should have been modified when valproate was substituted for phenytoin. However, the patient's clinical status was satisfactory on this regimen for several months before decompensation. The measurement of lamotrigine blood levels was useful in highlighting a possible cause of encephalopathy and in guiding the subsequent improvement. We suggest that lamotrigine should be considered as a cause of unexplained encephalography in patients taking it, particularly in combination with sodium valproate.

We thank A Richens for his helpful criticism.

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1 Richens A, Yuen AW. Overview of the clinical efficacy of lamotrigine. *Epilepsia* 1991; **32** (suppl 2): S13–16.
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Randomly amplified polymorphic DNA analysis in suspected laboratory *Helicobacter pylori* infection

SIR—Matysiak-Budnik and colleagues[1] reported a case of accidental ingestion of *Helicobacter pylori* in the laboratory. The incident involved a laboratory strain, but they did not isolate the strain causing the symptoms.

We report a case of infection of a bacteriologist, also involved in *H pylori* research. She had no history of gastrointestinal disease, and was *H pylori* seronegative 4 months earlier. She had an attack of severe epigastric cramp, accompanied by nausea and fever at 38°C. 3 days later she underwent endoscopy, which revealed erosive gastritis; there was an inflammatory infiltrate with numerous polymorphonuclear cells. Culture was positive for an *H pylori* strain (S1) sensitive to macrolides, amoxycillin, and metronidazole (1 mg/L). The patient was treated with amoxycillin (2 g daily) and clarithromycin (500 mg daily) for 10 days, and lansoprazole (30 mg daily) for 1 month.

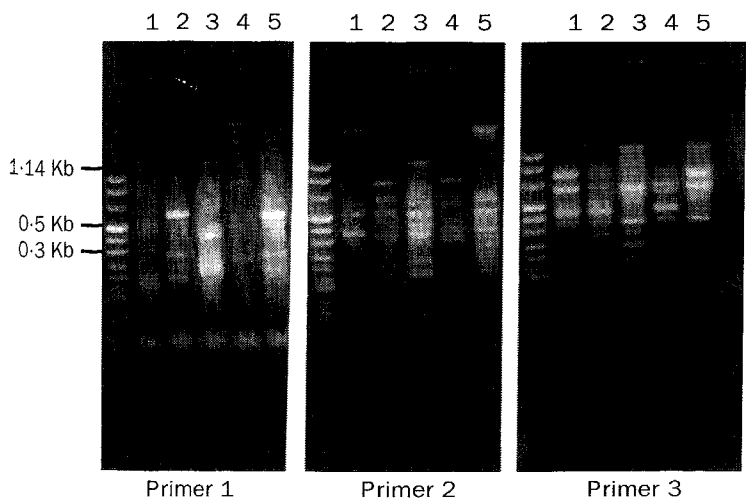

Figure: ***H pylori* DNA fingerprinting by RAPD**
Lane 1, strain S1 (subject); lane 2, strain S2; lane 3, strain S3; lane 4, strain S4; lane 5, strain S5. Numbers on left are reference molecular size markers (basepairs). First primer was 5'GCCCCCAGGGGCACAGT3', second primer was 5'AGTCAGCCAC3', and third primer was 5'TGGGAGGTGTATAGTCTA3'.

Symptoms disappeared 24 h after the start of treatment. A ^{13}C-urea breath test done 1 week after the end of treatment was negative. Serum was collected at days 5, 15, 30, and 45. No antibody to *H pylori* was detected by ELISA (Cobas Core 2nd G, Roche, France) probably because of the early treatment.

Assuming that the incubation period after ingestion is between 7 and 10 days[2] we did DNA fingerprinting by randomly amplified polymorphic DNA analysis (RAPD), as previously described,[3] of its own strain and the four other strains with which the patient had worked for 2 months earlier (S2, S3, S4, S5). The five strains produced distinct patterns (figure). We cannot exclude an infection caused by a strain that could not be isolated (coccoid form). However, without molecular study of such strains, laboratory infection cannot be proven, especially since the prevalence of *H pylori* infection is 25–45% in the general population.[4]

We thank A Lecomte for doing the endoscopy.

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1 Matysiak-Budnik T, Briet F, Heyman M, Megraud F. Laboratory acquired *Helicobacter pylori* infection. *Lancet* 1995; **346:** 1489–90.
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Alzheimer's disease in twins

SIR—Räihä and colleagues (March 2, p 573)[1] contemplated the genetic contribution in Alzheimer's disease (AD) in a Finnish twin cohort and reported a significantly higher incidence in monozygous (MZ) compared with dizygous (DZ) twin individuals with an adjusted monozygous/dizygous incidence ratio of 1·8 (95% CI: 1·2–2·7). A higher frequency in monozygous twin individuals was also seen in Parkinson's disease, multiple slcerosis, and in systemic rheumatic diseases. The pairwise concordance for AD was 18·6% in monozygous pairs and 4·7% in dizygous pairs. In line with prevailing opinion, they interpret their findings as a confirmation of the major genetic component for AD. However, the low concordance rate (18% instead of an expected 100%), is hard to reconcile with the genetic paradigm. Therefore, they admit the importance of identifying environmental triggers, eg, in utero experiences, including origins, placentation pattern, and fetal circulation circumstances.

Their conclusion concerning the genetic contribution would be attractive provided monozygous twinning and teratogenicity were independent phenomena. This, however, seems not to be valid. Experimentally-induced ageing of amphibian eggs before ovulation and/or fertilisation leads to axial duplication and even to mono-ovular twins, but also to degenerative changes and deficiencies in organogenesis, particularly of neurulation (disordered migration, resorption, failure of normal differentiation).[2,3] In mammals, including human beings the same tendency towards monozygous twinning and developmental abnormalities has been reported following delayed ovulation.[4] Interdependency of monozygous twinning and AD may therefore account for the too low concordance rate in monozygous twin individuals found by Räihä and colleagues.

The association of non-familial and late-onset AD and, to some extent also, of monozygous twinning with conditions related to non-optimal maturation and fertilisation of the oocyte, has been reported, ie, first and/or high birth order, very young and/or advanced maternal age, winter birth excess, specific constitutions (eg, reduced cognitive reserve capacity, proneness to aneuploid pregnancies). These environmental triggers may indicate that the quality of the oocyte at conception[5] is related to monozygous twinning and future AD. They have to be separated from the genetic contribution in AD, particularly in non-familial and late-onset AD, as in many other constitutional diseases of so-called multifactorial or polygenic origin.

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5 Jongbloet PH. Prepregnancy care: background biological effects. In: Chamberlain G, Lumley J, eds. Prepregnancy care: a manual for practice. Chichester: John Wiley, 1986: 31–52.

SIR—We tried to corroborate in Danish registers[1,2] the report by Räihä and colleagues (March 2, p 573)[3] of a higher frequency of Alzheimer's disease (AD) in individuals from monozygotic twin pairs, compared with individuals from dizygotic twin pairs. Furthermore, we compared the cognitive functions of elderly monozygotic and dizygotic twins using an interview-survey from 1995 among all Danish 75+ year old twins. In this age group AD comprises more than half the dementia cases.[4]

In our study all twins included were same-sexed and born before Feb 1, 1920. The Danish Hospital Discharge Register was established in 1977 and therefore only the 7144 twin individuals with known zygosity, who survived to 1977, were included. Of these 2690 survived to be eligible for the 1995 interview survey. We have previously reported that mortality trajectories throughout adulthood are similar in monozygotic and dizygotic individuals.[1] In the Danish register, dementia cases were sought under the same international classification of diseases (ICD) codes as in the Finnish study. The ICD group 290 consisted virtually only of "dementia senilis" diagnoses and it is therefore presented as one group in our table. Encephalopathy (ICD 781.79) was found only in six cases. Because we did not validate diagnoses through medical records, we excluded the ICD code 440.99 (generalised arteriosclerosis), which was found to be the major source of misclassification in the Finnish study. The table shows the nearly identical hospitalisation pattern for monozygotic and dizygotic individuals.

In the interview-survey the proportion of responders, responders by proxy and non-responders was similar for monozygotic and dizygotic individuals (73:7:20 *vs* 74:6:20). Furthermore, the proportion where dementia was given as reason for proxy-interview or non-response was similar in monozygotic and dizygotic twins (4·9% *vs* 4·6%, p>0·5). In the table the mini mental state cognitive screening examination (MMSE) scores[5] of those individuals who had physical impairments (which might affect their score) are excluded, together with those individuals who were reluctant to participate in the test. Inclusion of these individuals in the MMSE distribution also failed to show any significant difference in cognitive functions between monozygotic and dizygotic individuals.

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	Monozygotic	Dizygotic
Hospital Discharge Register 1977–94:		
Number of individuals	2546	4598
Mean age in 1977 (SD)	68·4 (7·8)	67·9 (7·7)
Number hospitalised 1977–94 (%)	2168 (85·2)	3886 (84·5)
Number (%) with ICD-codes		
290 (dementia senilis)	98 (3·8)	188 (4·1)
437 (diffuse cerebrovascular ischaemic disease)	90 (3·5)	160 (3·5)
Interview-survey 1995:		
Number completing MMSE	550	1024
Mean age (SD)	80·0 (4·0)	80·2 (4·2)
MMSE-score		
Number of individuals (%)		
MMSE 26–30	330 (60·0)	635 (62·0)
MMSE 24–25	100 (18·2)	181 (17·7)
MMSE 21–23	75 (13·6)	127 (12·4)
MMSE 18–20	29 (5·3)	50 (4·9)
MMSE <18	16 (2·9)	31 (3·0)

Table: **Danish same-sex twins born before Feb 1, 1920**

1 Christensen K, Vaupel J, Holm NV, Yashin AI. Mortality among twins after age 6: fetal origins hypothesis versus twin method. *BMJ* 1995; **310:** 432–36.
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Human diploid-cell rabies vaccine: efficacy of four doses

SIR—Rabies is a major health hazard and an economic burden for developing countries. Because of the cost of the human diploid-cell rabies vaccine (HDCV), Semple-type vaccines remain the usual treatment for patients bitten in these areas of the world. Unfortunately, neuroparalytic reactions are common with Semple-type vaccines,[1] resulting in about 20% fatalities.

We compared serum rabies virus neutralising antibody (SRVNA) titres of 23 adults vaccinated following exposure to a rabid dog; none had received a rabies vaccine in the past 10 years. They were immunised with five, 1 mL intramuscular doses of HDCV (Merieux Inactivated Rabies Vaccine, Pasteur Merieux Serums and Vaccines, Lyon, France), according to the recommendations of the World Health Organization.[2] Blood samples were taken at 16 and 45 days, after the fourth and fifth doses of the vaccine. SRVNA titres of double-blind coded sera were determined by the rapid fluorescent focus inhibition test.[3] Titres were adjusted to international unit/mL (IU/mL) with US Standard Human Immune Globulin R3 as a reference serum. Mean SRVNA titres after the fourth vaccination

	SRVNA levels	
	Fourth doses	Fifth doses
Subjects (n)	23	23
Mean (SD)	53 (36)	16 (24)*
Median	60	7·5*
Range	15–120	3·75–120

*p<0·01.

Table: **SRVNA (IU/mL) after fourth and fifth doses of HDCV**

The association of non-familial and late-onset AD and, to some extent also, of monozygous twinning with conditions related to non-optimal maturation and fertilisation of the oocyte, has been reported, ie, first and/or high birth order, very young and/or advanced maternal age, winter birth excess, specific constitutions (eg, reduced cognitive reserve capacity, proneness to aneuploid pregnancies). These environmental triggers may indicate that the quality of the oocyte at conception[5] is related to monozygous twinning and future AD. They have to be separated from the genetic contribution in AD, particularly in non-familial and late-onset AD, as in many other constitutional diseases of so-called multifactorial or polygenic origin.

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