Research letters

No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study

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Concern[1] of potential loss of confidence in measles, mumps, and rubella (MMR) vaccine has been raised by a recent paper[2] that suggested a causal association between this vaccine (or another environmental trigger) and a new syndrome of chronic inflammatory bowel disease and autism. Characteristically, all children described developed intestinal symptoms within days or soon after vaccination.

The National Board of Health and National Public Health Institute launched a long-term vaccination project in 1982, which aimed at the elimination of MMR diseases from Finland.[3] All children are vaccinated twice, at age 14–18 months and 6 years; further vaccinations are carried out among recruits of the defence forces and in some schools of nursing. Only one type of live-virus vaccine (MMR or Virivac [Merck, West Point, PA, USA]) consisting of the more attenuated Enders Edmonston, Jeryl Lynn, and Wistar RA 27/3 strains for measles, mumps, and rubella, respectively, has been used since beginning of the project. Adverse events in temporal relation to MMR vaccine were reported prospectively to the Institute. A form was filled and posted to us, followed by another form with further information 2–3 weeks later. We traced those vaccinees who developed gastrointestinal symptoms or signs lasting 24 h or more at any time after MMR vaccination (apart from within the first hour). We checked hospital or health centre records or interviewed the local public-health nurses.

By the end of 1996, about three million vaccine doses had been delivered by the Institute. 31 children developed gastrointestinal symptoms after vaccination (table); all except one after the first vaccine dose. *Haemophilus influenzae* type b conjugate vaccine was given concomitantly in four cases. 20 patients were admitted to hospital. Antibiotics were given in 11 cases, symptomatic relief in nine, and intravenous γ-globulin was given to one child with Guillain Barré syndrome.

The time between the reported event and our check on their health varied from 1 year and 4 months to 15 years and 1 month. The mean interval was 9 years 3 months, the median being 10 years and 8 months.

Diarrhoea, frequently with vomiting, was the most common symptom (55%, n=17), followed by gingivostomatitis (23%, n=7), vomiting only (16%, n=5), and abdominal pains (n=2). The time from MMR vaccine to onset of symptoms varied from 20 h to 15 days. Duration of symptoms was not always stated or recalled by nurses, but subsidence within a week was usual, except in a 1-year-old boy (patient 23) whose diarrhoea lasted for 6 weeks. The child recovered and was healthy when checked almost 6 years later. Most symptoms and signs of the central nervous system were those one would expect in conjunction with acute gastrointestinal disease: five (16%) children had febrile seizures and two had headache. One child developed ataxia

Child	Sex	Vaccination		Interval from vaccination to intestinal symptoms	Symptoms other than intestinal	Duration of intestinal symptoms	Admitted to hospital	Time elapsed until check-up
		Year	Age					
1	M	1982	6 yr 11 mo	≈1 week	Fever, seizure, pneumonia	<1 week	Yes	11 yr 3 mo
2	F	1982	1 yr 9 mo	5 days	Fever, tonsillitis	3 days	Yes	9 yr
3	F	1982	6 yr 11 mo	1 day	Fever, headache	≈4 days	No	7 yr
4	M	1982	1 yr 6 mo	2 days	Fever, respiratory	≈1 week	Yes	5 yr 9 mo
5	F	1983	1 yr 5 mo	9 days	. .	Not stated	Yes	15 yr 1 mo
6	F	1983	1 yr 2 mo	9 days	Fever, seizure	≈2 days	Yes	15 yr 1 mo
7	M	1983	6 yr 11 mo	13 days	Fever	5 days	Yes	15 yr 1 mo
8	F	1983	6 yr 5 mo	10 days	Fever, otitis, headache	Not stated	No	14 yr 11 mo
9	M	1983	1 yr 6 mo	11 days	Fever, rash, pneumonia	Not stated	Yes	14 yr 9 mo
10	M	1983	1 yr 3 mo	13 days	Fever, seizure, rash	5 days	Yes	14 yr 8 mo
11	F	1983	1 yr 3 mo	4 days	Fever, rash	Not stated	Yes	14 yr 6 mo
12	F	1983	1 yr 3 mo	4 days	Fever, seizure, otitis	1 week	Yes	14 yr 5 mo
13	M	1983	2 yr 7 mo	8 days	Fever, lymphadenopathy	Not stated	No	13 yr 8 mo
14	F	1983	4 yr 6 mo	6 days	Fever, probable pneumonia	5 days	Yes	13 yr 7 mo
15	F	1984	3 yr 11 mo	20 h	Fever, rash	Not stated	Yes	14 yr
16	F	1984	1 yr 3 mo	3 days	Fever, seizure	1 week	Yes	13 yr 9 mo
17	M	1984	1 yr 7 mo	≈2 weeks	. .	Not stated	No	4 yr
18	M	1985	1 yr 4 mo	3 days	Fever, tonsillitis	Not stated	Yes	11 yr
19	M	1985	1 yr 9 mo	5 days	Fever, lymphadenopathy	Not stated	Yes	7 yr 11 mo
20	F	1986	6 yr 10 mo	3 days	Fever, pneumonia, otitis	3 days	Yes	11 yr 5 mo
21	M	1987	1 yr 7 mo	9 days	Fever, rash, conjunctivitis, otitis	≈1 week	No	10 yr 8 mo
22	F	1989	2 yr 2 mo	4 days	Fever, respiratory	2 days	Yes	2 yr 10 mo
23	M	1991	1 yr 5 mo	7 days	Fever, rash, probable orchitis	6 weeks	No	5 yr 7 mo
24	F	1992	13 yr	3 days	Fever, urticaria, conjunctivitis	≈2 days	No	6 yr 1 mo
25	F	1993	1 yr 2 mo	15 days	Urticaria	≈2 days	Yes	4 yr 7 mo
26	M	1993	1 yr 5 mo	11 days	Fever, rash	6 days	No	4 yr 7 mo
27	M	1994	1 yr 9 mo	11 days	Fever, rash	≈2 days	No	3 yr 8 mo
28	F	1995	1 yr 5 mo	5 days	Fever, ataxia	4 days	Yes	2 yr 7 mo
29	M	1995	1 yr 6 mo	13 days	Fever, urticaria	≈2 days	No	1 yr 7 mo
30	F	1996	1 yr 7 mo	Not stated	Fever, rash	Not stated	Not stated	1 yr 9 mo
31	M	1996	1 yr 7 mo	11 days	Fever, Guillain Barré	5 days	Yes	1 yr 4 mo

Characteristics of patients with gastrointestinal and other symptoms after MMR vaccination

which subsided quickly. No child developed autistic-spectrum disorder. Hyperornithaemic gyrate atrophy, an autosomal recessive disease, was diagnosed in one girl (patient 14) 8 years after vaccination. A boy developed *H influenzae* meningitis, and a girl meningococcal meningitis 1 day and 7 days after vaccination, respectively.

It is noteworthy that, besides gastrointestinal complaints, many children had similar symptoms and signs (fever, rash, seizure) as those in London.[2] Presumably, some patients with symptoms or signs not far from those listed in the table were not reported to us. We do not deem this shortcoming to be of a major concern because illness in all our 31 patients was mild, and probably sometimes caused by concomitant infection.[4]

Over a decade's effort to detect all severe adverse events associated with MMR vaccine could find no data supporting the hypothesis that it would cause pervasive developmental disorder or inflammatory bowel disease.

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Severe premature coronary artery disease with protease inhibitors

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Until recently, the prognosis for people with AIDS was so poor that concerns about other long-term health problems seemed irrelevant. The introduction of antiretroviral treatment with protease inhibitors has had a profound impact on mortality from AIDS.[1] After two young AIDS patients on protease inhibitors under our care developed coronary artery disease, we examined lipid abnormalities among HIV-1-infected people receiving protease inhibitors and designed an intervention based on the National Cholesterol Education Program (NCEP) guidelines.[2]

A 26-year-old HIV-1-infected man (CD4 T cell count <10 cells/μL) was admitted with angina. He had a history of cigarette smoking and occasional cocaine use (none recently). The plasma HIV-1-RNA level was more than 1 000 000 copies/mL, so 4 weeks before admission he was started on directly-observed ritonavir, saquinavir, lamivudine, and stavudine. Coronary angiography showed a large occlusive thrombus within the right coronary artery.

A 37-year old HIV-1-infected man presented with angina after shovelling snow. His lowest CD4 T-cell count was 14 cells/μL with a peak plasma HIV-1 RNA level of 685 000 copies/mL. He had developed cytomegalovirus retinitis and diabetes mellitus before starting protease inhibitors at age 35. He had a family history of heart disease but no history of cigarette smoking. His cholesterol concentration increased from 4·28 mmol/L before starting indinavir to 8·46 mmol/L 5 months later. 7 months before presentation his fasting cholesterol was 12·3 mmol/L, high-density cholesterol (HDL) 0·46 mmol/L, and triglycerides 22·14 mmol/L, while his plasma HIV RNA level was <500 copies/μL. He developed a right cervical region fat pad. He was taking gemibrozil 600 mg orally twice daily, aspirin, indinavir, zidovudine, and lamivudine. Coronary arteriography revealed occlusion of the left anterior descending artery and severe atherosclerosis involving the right coronary artery.

A review of 124 patients on protease inhibitors in our HIV clinic identified 41 (33%) with raised lipid concentrations who were referred for NCEP intervention. For 15 patients (mean fasting lipids-cholesterol 6·35 mmol/L; triglycerides 3·6 mmol/L), a diet exercise programme was instituted. 26 patients (mean fasting lipids-cholesterol 8·98 mmol/L; mean triglycerides 19·2 mmol/L) were referred for drug treatment (gemfibrozil for 3 months then atorvastatin).

Peripheral lipodystrophy has been reported in patients receiving protease inhibitors.[3,4] In one study, metabolic abnormalities (higher triglyceride, cholesterol, insulin, and C-peptide levels, and insulin resistance scores) were described in 72 (64%) of 116 patients after a mean 10 months on treatment.[5] Clinicians need to be aware of the potential for accelerated atherosclerosis in patients treated with protease inhibitors. For now, we obtain a fasting lipid profile before and then 3–6 months after the start of protease inhibitor therapy and then use NCEP guidelines to treat abnormalities identified.

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Hormone-receptor status of breast cancer in Papua New Guinea

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The survival of women with breast cancer varies with racial background and geographical location. Whilst black women have a higher mortality than white women, the causes of racial difference in breast tumour biology are unknown.[1] The well-known association between oestrogen (ER) and progesterone (PR) receptor status and both response to tamoxifen treatment and prognosis has prompted several

Racial origin	ER+ PR+	ER+ PR−	ER− PR+	ER− PR−
White*	59	15	6	20
Black*	44	14	7	35
New Guinea Melanesian	4	4	38	54

*Data from Gapstur et al.[2]

Percentage incidence of oestrogen and progesterone receptors in breast tumours

studies of the distribution of these receptors among breast tumours in patients of different racial origins.[2] Informal observation of indigenous Papua New Guinean patients treated at Lae and Port Moresby hospitals in the past few years has revealed the frequent occurrence of the more aggressive tamoxifen-resistant forms of breast cancer similar to that in black populations. We therefore conducted a study of the hormone-receptor status and age incidence of our breast cancer patients.

Formaldehyde-fixed and paraffin-embedded archival breast cancer removed from patients between January, 1995, and March, 1997, were stained by conventional immunohistochemical methods with the Dako ER/PR test kit for PR and ER receptors, and scored by use of standard histopathological criteria.[3] The quality of all biopsy material was confirmed by strong reactivity with the Vimentin monoclonal antibody by immunohistochemistry. Of the 26 specimens examined, 11 were positive for PR and two for ER, one was positive for both receptors (table). To allow comparison with data from western populations (with a different assay method, the quantitative hormone-receptor assay), we present equivalent percentages extracted from Gapstur and colleagues.[2]

81% of our patients were premenopausal, which is in close agreement with the findings of Sen Gupta and co-workers (1990)[4] for breast cancer in Papua New Guinea, where 80% of patients were under 50 years of age. A similar age incidence was found for breast cancer in black Africans in Zimbabwe,[5] although hormone-receptor status is not recorded for this group of patients.

Although our sample is small and uncontrolled, our results reveal a pattern of hormone receptors, atypical of known racial and social factors. The popularity of continuous uncontrolled parenthood and the frequent concurrence of breast cancer with pregnancy or lactation could, in part, explain the low proportion of ER-positive PR-positive tumours in the study population. However, the unique racial and cultural background of the indigenous Papua New Guinean Melanesians may contribute to the abnormally high proportion of ER-negative PR-positive tumours. If this pattern is related to a genuine biological difference in tumour biology, it could provide a genetic basis for the poor prognosis of premenopausal breast cancer and an opportunity for new approaches to management.

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Presence of donor-specific DNA in plasma of kidney and liver-transplant recipients

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The development of microchimerism after transplantation is well recognised[1] and may contribute towards graft acceptance.[2] We have shown that DNA from fetuses is present in the plasma of their mothers,[3] and now suggest that, in transplant patients, DNA from the organ donor may also be present in the plasma of the recipient.

Women who had had liver or kidney transplants were recruited from the Department of Surgery, Prince of Wales Hospital and the Department of Medicine, Princess Margaret Hospital, Hong Kong, respectively. Approval of the project was obtained from the Clinical Research Ethics Committee of The Chinese University of Hong Kong. 5 mL of venous blood was collected in tubes containing edetic acid, and separated into plasma and buffy coat.[3] DNA from plasma and buffy coat samples were extracted with a QIAamp Blood Kit (Qiagen, Hilden, Germany) according to the blood and body-fluid protocol recommended by the manufacturer.[4] 400–800 μL plasma or 200 μL buffy coat was used for DNA extraction per Qiagen column. 10 μL (out of an elution volume of 50 μL) of DNA extracted from plasma or 1 μg of DNA extracted from buffy coat was subjected to 50 cycles of Y-specific PCR with primers Y1·7 and Y1·8.[3] PCR products were analysed by agarose-gel electrophoresis and ethidium-bromide staining.

Samples from eight women who had had liver transplants and 28 who had had kidney transplants were analysed. For the six liver-transplant recipients with male donors, plasma and cellular chimerism was found in six (100%) and five (83%) patients, respectively. For the 17 kidney-transplant patients with male donors, the corresponding figures were 14 (82%) and four (24%). None of the 13 liver and kidney transplant patients with female donors had Y-specific sequences.

These results show that donor-specific DNA sequences are present in the plasma of most liver and kidney transplant patients. This finding has not previously been reported, probably because plasma is routinely discarded in the early steps of many DNA extraction methods. Because it is a cell-death marker,[5] plasma donor DNA may be released from necrotic or apoptotic cells in the transplanted organ or donor-derived haemopoietic cells in the recipient's blood or other organs. In 11 cases, plasma donor DNA was detected even though no cellular chimerism was seen in the recipient's blood, suggesting that plasma DNA chimerism in these patients originates from the transplanted organ or from donor's haemopoietic cells residing in tissues other than blood.

Since graft rejection is an important cause of cell death in the transplanted organ, our observations raise the possibility that the concentration of donor DNA in the recipient's plasma may be a marker for rejection. Apart from cell death secondary to graft rejection, other causes of tissue damage in the transplanted organ would also be expected to result in the liberation of DNA in the plasma. Examples include infections affecting the graft, for example, cytomegalovirus, biliary (for liver transplantation) and vascular complications, and neoplastic involvement of the transplanted organ. It would also be useful to evaluate the effect of various immunosuppressive regimens on the concentration of donor DNA in the recipient's plasma. Future work with quantitative PCR on serial samples from transplant patients

will be necessary to address these issues and may improve our understanding of the immunology of organ transplantation.

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A urinary marker for multiple sclerosis

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A toxic factor for macroglial cells has been described in monocyte cultures in vitro and in cerebrospinal fluid (CSF) from multiple sclerosis (MS) patients, as reported in the first communication.[1] This gliotoxic activity is a form of apoptosis and can be detected by a diethyl-tetrazolium salt-based in-vitro assay. Having established a flow-cytometry procedure to detect staurosporine-induced apoptosis in immortalised glial cells, we have applied this method to optimisation of gliotoxic activity detection in body fluids.* This gliotoxic activity was related to a protein of molecular weight 17 kDa. Since other data indicated passage from CSF to blood, we supposed that glomerular passage of this protein was also possible. We identified gliotoxic activity associated with a protein with identical biochemical characterstics to that in urine from patients with MS.

We studied urine samples because they are easy to obtain and allow extensive and repeated sampling, which is not practical or ethical with CSF. Total urine (50 μl per well) was heated at 56°C for 30 min, passed through 0·2 μm filter, directly added to cell-culture wells, and incubated for 72 h. After DNA strand-break extraction and propidium iodide staining, apoptosis was measured by comparison with normal proliferating cells. We report our initial findings of gliotoxic activity in urine from 104 individuals. For patients in hospital, urine was collected immediately on admission before the start of treatment. Group 1 included 35 patients with definite MS according to Poser's criteria.[2] The clinical course and status were described with the EDMUS impairment scale.[3] Group 2 included 34 patients with other neurological disorders: 25 with central nervous system illnesses, eight with peripheral nervous system disease, including inflammatory neuropathies, and one psychiatric patient. Group 3 consisted of 35 healthy volunteers. Urinary gliotoxic activity was tested twice independently in all individuals.

The results are shown in the table. 32 of 35 patients with MS had a positive test—ie, glial cell apoptosis induced by urine. The three cases with negative findings had a disease duration of less than 10 years, with an attack at the time of sampling but a low disability score. Nevertheless, these characteristics did not suggest a particular clinical profile, since they were also found in two other MS patients with a positive test. All healthy controls had a negative test as did 33 of 34 patients with other neurological diagnoses. The only exception was a patient with benign fasciculations.

	MS urine	Non-MS urine	
	Mulltiple sclerosis (n=35)	Other neurological disorders (n=34)	Healthy controls (n=35)
Apoptosis	32/35 (91%)	1/34 (3%)	0/35 (0%)
No apoptosis	3/35 (9%)	33/34 (97%)	35/35 (100%)

Detection of apoptosis induced on an immortalised macroglial cell line by urine samples from MS patients, non-MS patients, and healthy controls

Our results show a strikingly high sensitivity (91%) and specificity (97%) of this urinary marker in MS. It is worth noting the negative results in patients with other neurological diseases, including Guillain-Barré syndrome, centropontine myelinolysis, and brain glioblastoma. During the past 20 years, several investigators have failed to identify a suitable biological marker of multiple sclerosis, including myelin basic protein.[4] We demonstrate here that this gliotoxic factor can simply and repetitively be detected without invasive sampling. Our findings may be useful in the diagnosis or the follow-up of MS, and may help to assess therapeutic strategies. It might be interesting to correlate urine gliotoxic activity with magnetic-resonance-imaging-detected brain and spinal cord lesions, as well as with the intensity of relapses. The characterisation of the peptide sequence of this gliotoxic factor, which may be a glycoprotein, is now a priority.

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*Detailed protocol available from the authors, on request.

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HSV-1 in brain and risk of Alzheimer's disease

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We have shown that the incidence of herpes simplex virus 1 (HSV-1) in the brain is similar in elderly individuals with and without Alzheimer's disease (AD).[1] We have also shown that individuals carrying the ε4 allele of apolipoprotein E (apoE) are at increased risk of developing AD.[2] Itzhaki and colleagues[3] have shown that the combination of HSV-1 in the brain and presence of the ε4 allele of apoE together confer an even greater risk for AD when compared with individuals carrying the ε4 allele alone.[3]

We investigated brains from 73 elderly individuals with neuropathologically confirmed AD (34 men, mean age 77·2 [range 53–93] years) and 33 without AD (27 men, mean age 72·2 (43–95] years) based on criteria established by

	Patients without AD (n = 33)			Patients with AD (n = 73)		
	HSV-1 positive	HSV-1 negative	Total	HSV-1 positive	HSV-1 negative	Total
Genotype						
ε2/ε2	0	0	0	0	0	0
ε2/ε3	3	2	5	0	0	0
ε2/ε4	0	0	0	2	0	2
ε3/ε3	16	7	23	21	10	31
ε3/ε4	5	0	5	24	9	33
ε4/ε4	0	0	0	7	0	7
Allele frequency						
ε2	6·3%	11·1%	7·6%	1·9%	0·0%	1·3%
ε3	83·3%	88·9%	84·9%	61·2%	76·3%	65·1%
ε4	10·4%	0·0%	7·6%	37·0%	23·7%	33·6%

Susceptibility to HSV-1 infection in patients with and without AD

Khachaturian.[4] DNA was extracted from brain tissue and used as a template to amplify by PCR a 138 bp fragment from the glycoprotein D gene of HSV-1.[1] ApoE genotype was determined with allele-specific primers. Brain samples were classified as HSV-1-positive or HSV-1-negative. HSV-1-positive patients were defined as those with at least one of five brain regions positive for HSV-1. Most HSV-1-positive patients were positive in all five brain regions examined.

There was no significant difference in the observed apoE ε4 allele frequency between HSV-1-positive AD patients and HSV-1-negative patients (37% *vs* 24%, p = 0·19 by χ^2). There were insufficient samples to complete a valid χ^2 analysis for the control group. HSV-1-positive ratio did not differ significantly between AD patients and controls (74% *vs* 73%, p=0·89). No increased susceptibility to HSV-1 infection was found among apoE ε4 allele carriers compared with non-ε4 carriers, irrespective of pathology (81% *vs* 68%, p=0·20) (table).

In contrast to the results of Itzhaki et al,[3] our findings suggest that HSV-1 does not confer increased risk for AD when combined with the presence of an ε4 allele of apoE, that HSV-1 alone is not an independent risk factor for AD, and that apoE ε4 allele carriers are not more susceptible to HSV-1 infection than non-carriers. One possible explanation for the difference between the datasets could be the prevalence of the ε4 allele in the AD populations examined. The apoE ε4 allele frequency in late-onset sporadic AD has been established at 36·7%.[5] In the work of Itzhaki et al,[3] the ε4 allele frequency among AD individuals was 43·5%, whereas in our study it was only 33·6%. Further studies are required on a larger number of individuals, especially healthy individuals carrying an apoE ε4 allele.

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Improvement in renal cholesterol emboli syndrome after simvastatin

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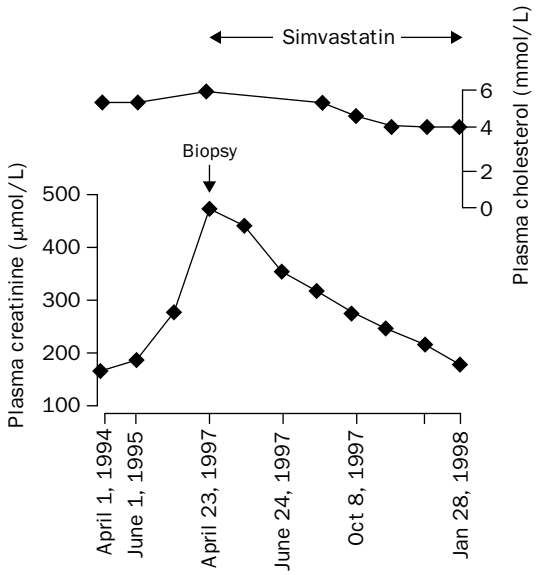
The clinical presentation of systemic cholesterol emboli syndrome is protean with both local and systemic symptoms and signs. Renal involvement is common and although commonly precipitated by angiography or other vascular instrumentation, it can occur spontaneously in patients with aortic atherosclerosis.[1,2] There is no specific treatment, although aggressive blood pressure lowering is recommended and anticoagulation contraindicated.[3] Here we describe a patient with proven renal cholesterol emboli, in whom progressive renal dysfunction was halted and then reversed after treatment with simvastatin.

A 68-year-old Asian man was referred with a 5-year history of raised erythrocyte-sedimentation rate (ESR), anaemia, chronic progressive renal impairment, and intermittent fevers. Hypertension had been diagnosed in 1973 and the patient sustained a small left occipital infarct in 1990. In 1992, he was referred to a chest physician with a history of night sweats, weight loss, and chest discomfort. Investigations revealed a normal chest radiograph, haemoglobin (Hb) 12 g/dL, and ESR 63 mm/h; both tuberculosis and myeloma were excluded. In April, 1994, chest pain led to a cardiology referral and exercise electrocardiography, during which the patient sustained an inferior infarct. At that time his plasma creatinine was 165 μmol/L, fasting glucose 4·6 mmol/L, cholesterol 5·3 mmol/L, and triglycerides 1·4 mmol/L. In June, 1995, he was seen by a gastroenterologist with intermittent diarrhoea. Barium studies were normal. On March 1, 1997, he was admitted with a short history of chest pain, anorexia, weight loss, general malaise, and fevers. Investigations revealed Hb 10·5 g/dL, ESR 120 mm/h, creatinine 275 μmol/L, and 0·46 g proteinuria per day. An abdominal ultrasound showed both kidneys to be irregular with a bipolar length of 9 cm. The aorta was noted to be ectatic but not aneurysmal. His symptoms resolved and he was discharged without a diagnosis but was readmitted 4 weeks later with severe back, thoracic, and loin pain, and painful cold cyanotic feet. Plasma creatinine had risen to 434 μmol/L and fasting cholesterol was 5·8 mmol/L. Renal biopsy was done on April 10, 1997, and revealed cholesterol clefts in interlobular arteries and focal interstitial atrophy



Plasma creatinine and cholesterol before and after simvastatin

with lymphocyte infiltration. Simvastatin 10 mg daily was started (increased to 40 mg over 3 months). The patient had severe rest pain in his cyanotic feet requiring opiate analgesia and a lumbar sympathectomy was done on June 27, 1997, with minor benefit. Over the following weeks, the circulation to his feet improved, his analgesic requirement reduced, and his renal function improved progressively. By January 28, 1998, his plasma creatinine was 177 μmol/L and random cholesterol 4·1 mmol/L (figure).

In this case of histologically proven spontaneous renal cholesterol emboli syndrome, progressive renal insufficiency was reversed after the introduction of simvastatin in the absence of substantial hypercholesterolaemia. We propose that simvastatin stabilised cholesterol-rich aortic atherosclerotic plaques which had been showering cholesterol emboli into both renal and pedal circulations. Although the successful treatment of cyanotic toes (secondary to cholesterol emboli) with lovastatin[4] and of systemic cholesterol embolic disease with cholestyramine and probucol[5] has previously been reported, progressive improvement of renal function has not been documented. Functional improvement of the renal and pedal circulations presumably followed recanalisation of arterioles previously obstructed by cholesterol emboli.

The diagnosis of renal cholesterol emboli has previously been associated with a grave prognosis[1] but this case suggests possible benefit from simvastatin. Statin therapy could also have a preventive role in the pretreatment of high-risk patients scheduled to undergo vascular intervention

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Health anxiety in medical students

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Clinical teachers report that medical students frequently develop fears and symptoms of illness. This has been termed medical student's disease, nosophobia, hypochondriasis of medical students, and medicalstudentitis.[1,2] Such reactions may be best conceptualised as a mild form of health anxiety[3] or transient hypochondriasis.[4] Students often seek reassurance from their own doctor, sometimes involving needless medical investigations. Associated distress may interfere with study. Health anxiety may therefore represent a poorly characterised occupational illness. Three studies have assessed this phenomenon. Two were carried out over 30 years ago and all were conducted in the USA. An uncontrolled study based on case records concluded that about 70% of medical students have groundless medical fears during training.[1] In the second study, of 33 randomly chosen medical students from 1 year, 78·8% had a history of "medical student disease".[2] In the only controlled study, carried out over 10 years ago, Kellner and colleagues[5] matched medical and law students (60 in each group), and found that medical students attended to their health and somatic symptoms more than law students but there was no significant difference in the rate of hypochondriasis.

	Medical students	Non-medical students	Non-students
Health anxiety	8·7 (4·1)	9·9 (4.6)	9·5 (4·9)*
Health concern	3·2 (1·9)	2·7 (1·6)	3·1 (2·4)*
Bodily awareness	1·2 (0·7)	1·5 (0·7)	1·5 (0·7)†
Perceived risk of illness	0·45 (0·7)	0·7 (0·6)	0·8 (0·7)†
Probability that treatment would be ineffective	1·2 (0·6)	0·9 (0·6)	1·2 (0·7)†

*p>0·01. †p<0·05.

Mean (SD) total health anxiety scores and details of three specific items

In January, 1996, a short illness behaviour questionnaire* (the Whitley index, a version of the Illness Behaviour Questionnaire) and the Short Health Anxiety inventory were distributed to all 306 clinical medical students at University of Oxford Medical School. No personal identifiers were asked for. During this time, a comparison group was surveyed which comprised all the students studying any subject except medicine at two Oxford University colleges.

183 (59·8%) medical students replied. 148 (48·4%) completed the questionnaire. 110 (non-medical) students completed questionnaires. Data on file for a general Oxford population was also used. An analysis of variance was carried out with SPSS. On total scores for the health anxiety questionnaires, medical students scored non-significantly lower than the other students and the non-students (p>0·1). An (uncorrected) item analysis for the 18 items on the health-anxiety inventory found significant effects for three items; in two of these, medical students were lower than the other two groups (awareness of bodily sensations or changes; perceived risk of illness; table). On perception of the likely effectiveness of medical treatment in the event of illness, non-medical students perceived treatment as more likely to be effective than the other two groups. The only other difference was that medical students were less likely to avoid seeking medical help.

These results question the widely held view that medical students are more likely than others to have excessive anxiety about their health. Two factors may contribute to the impression that this is a common reaction to medical training. First, the phenomenon of trainee doctors who falsely believe themselves to have an illness may receive more attention from and be more memorable to both tutors and the student's physician than the same phenomenon in a geology student. Second, the early claims of high prevalence (more than 70%) may have resulted in selective attention to the phenomenon and a lowered threshold for its recognition.

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*Copies of questionnaire can be obtained from PMS.

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