Letters

Diagnosing pulmonary embolism

Not all procedures are invasive

EDITOR—Tony Fennerty sets his review of the diagnosis of pulmonary embolism in the context where pulmonary angiography is not generally available.[1] This seems a rather backward looking approach as any modern radiology department performing angiography should be able to perform a pulmonary study. We believe that even when pulmonary angiography is freely available, it is not commonly requested by referring clinicians because they are reluctant to use an invasive procedure that they perceive as dangerous. However, pulmonary angiography with selective angiography using non-ionic contrast medium has a low mortality (<1%) and morbidity (2-5%).[2] Fennerty quotes a mortality of 0.1% from treatment with anticoagulants, but this is much lower than in other reported series (1-2% mortality, 5-25% morbidity),[2] which suggests that empirical anticoagulation should be avoided. Pulmonary angiography should be requested more often when isotope lung scans show an intermediate or low probability of pulmonary embolism and Doppler studies of the leg veins give negative results, especially when clinical suspicion is high.

Fennerty gives only a passing reference to the future role of fast computed tomography techniques, despite them having been shown to be as reliable as angiography or isotope scanning in detecting central pulmonary embolism, although not in detecting subsegmental acute emboli.[3] The exact role of fast computed tomography has yet to be established, but if available it is a non-invasive alternative to angiography after a non-diagnostic isotope study. If the scan is negative some centres may still perform angiography, but a positive scan avoids the need for angiography. Fast computed tomography has also been championed as a first line alternative to isotope scanning.[2] The only contraindication is a documented adverse reaction to intravenous iodinated contrast media.

Finally, Fennerty did not mention the possible future role of magnetic resonance imaging which is also evolving as a potential non-invasive means of directly depicting clots in the pulmonary artery. It is a particularly attractive prospect as it avoids iodinated contrast media and could be combined with magnetic resonance venography of the legs and pelvis for evaluation of deep vein thrombosis. Currently the sensitivity of magnetic resonance imaging for segmental pulmonary embolism is inferior to fast computed tomography.[4] However, its potential advantages necessitate its continued development.

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Three non-invasive techniques failed to get a mention

EDITOR—In his review Tony Fennerty aimed "to describe ways of diagnosing pulmonary emboli without resorting to angiography" yet failed to mention three non-invasive techniques that are increasingly available to clinicians in district general hospitals.[1]

Transthoracic cross sectional echocardiography and Doppler measurements commonly show evidence of right heart strain such as increased right ventricular end diastolic diameter, leftward bulging of the intraventricular septum in diastole, tricuspid regurgitation, and evidence of raised right atrial pressure such as a low collapse index of the inferior vena cava.[2] Sometimes emboli can be seen within the heart or main pulmonary vessels[3] although transoesophageal echocardiography is more sensitive.[4] Where echocardiography fits in to the diagnostic workup of patients with suspected pulmonary emboli depends on how quickly the test can be organised and how well operators can examine right sided structure and function.

Increasingly clinicians are requesting echocardiograms in suspected heart failure and also in atrial fibrillation. Pulmonary emboli should be strongly suspected if unexplained right ventricular enlargement or Doppler evidence of tricuspid regurgitation or pulmonary hypertension is detected in the absence of valve disease or left ventricular dysfunction in such patients.

Finally, spiral computed tomography will increasingly become available. It seems to have higher sensitivity and specificity than transoesophageal and transthoracic echocardiography. In a prospective series of 75 patients, 39 had evidence of pulmonary emboli on both pulmonary angiography and spiral computed tomography.[5] The prospective sensitivity was 91%, specificity 78%, positive predicted value 100%, and negative predicted value 89%, comparing favourably with pulmonary angiography.

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1 Fennerty T. The diagnosis of pulmonary embolism. *BMJ* 1997;314:425-9. (8 February.)
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Advice to authors

We receive more letters than we can publish: we can currently accept only about one third. We prefer short letters that relate to articles published within the past four weeks. We also publish some "out of the blue" letters, which usually relate to matters of public policy.

When deciding which letters to publish we favour originality, assertions supported by data or by citation, and a clear prose style. Letters should have fewer than 400 words (please give a word count) and no more than five references (including one to the BMJ article to which they relate); references should be in the Vancouver style. We welcome pictures.

Letters should be typed and signed by each author, and each author's current appointment and address should be stated. We encourage you to declare any conflict of interest. Please enclose a stamped addressed envelope if you would like to know whether your letter has been accepted or rejected.

We may post some letters submitted to us on the world wide web before we decide on publication in the paper version. We will assume that correspondents consent to this unless they specifically say no.

Letters will be edited and may be shortened.

Lung perfusion scanning is a useful diagnostic tool

EDITOR—Tony Fennerty supports the use of ventilation-perfusion scanning combined with clinical assessment for the diagnosis of pulmonary emboli[1] but does not include evidence from the prospective investigative study of acute pulmonary embolism diagnosis.[2] This study examined the role of lung perfusion scanning and clinical assessment in diagnosing pulmonary emboli. A positive scan was obtained in 92% of patients with a pulmonary embolus proved angiographically and a negative scan in 87% of patients without a pulmonary embolus. The specificity is therefore much higher than standard ventilation-perfusion scanning (10%).[3] By adopting the recommendations of these two studies, the need for pulmonary angiography may be reduced and the problem of non-diagnostic ventilation-perfusion scans avoided.

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Outcome depends on size of embolus

EDITOR—Although Tony Fennerty's review on the diagnosis of pulmonary embolism was concise and practically helpful,[1] we would like to draw attention to an often neglected point.

A diagnosis of pulmonary embolism is not enough. Major and minor pulmonary embolism must be clearly distinguished as they are quite different clinical entities. In the case of major pulmonary embolism, recurrence of even a small embolus may be immediately fatal. This danger does not exist with minor pulmonary embolism. For similar reasons, major and minor thrombi must be distinguished in a diagnosis of leg vein thrombosis. A large embolus may cause sudden death whereas a small one does not carry such a risk.

Any diagnostic workup in suspected pulmonary embolism should be considered complete only after assessing the residual capacity of the right ventricle to cope with additional obstruction of the lumen of the pulmonary artery and the size of a recurrent embolus. An unfavourable ratio of cardiopulmonary reserve to residual thrombus volume warrants a swift and aggressive approach. In such patients we strongly favour placement of a filter in the inferior vena cava, followed by thrombolytic treatment.

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Morbidity should be taken into account when deciding on anticoagulant treatment

EDITOR—Although Tony Fennerty provides a good review of the diagnosis and treatment of pulmonary embolism, we question the reliability of the quoted mortality of 0.1% associated with anticoagulant treatment for thromboembolic disease.[1] This rate is based on a study that investigated the optimum duration of treatment for thromboembolic disease in selected populations of hospital patients[2] and cannot be generalised to routine clinical practice. A mortality of 0.8% for all clinical conditions associated with oral anticoagulant treatment was reported in a review of observational studies.[3] To quote figures only for mortality and not morbidity for adverse events associated with oral anticoagulant treatment is misleading. Major bleeding events may develop in up to 12% of patients per year.[4] Morbidity will obviously impinge on any decision about anticoagulation for any clinical indication. There are disagreements, however, about the definitions of relative severity of associated morbidity.

We agree that the incidence of major adverse events seems to be decreasing, possibly because of improved control of the international normalised ratio. In a randomised controlled trial of the management of oral anticoagulant treatment in general practice we observed no fatalities in over 300 patient years of follow up,[5] which would accord with the low figure quoted by Fennerty.[1] Given the lower target therapeutic range of the international normalised ratio in treating pulmonary embolism, the incidence of serious adverse events should be lower in this group of patients, thus influencing the decision whether to give anticoagulants to patients with this condition.

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1 Fennerty T. The diagnosis of pulmonary embolism. *BMJ* 1997;314:425-9. (8 February.)
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Intravenous antibiotic treatment at home can provide higher quality care

EDITOR—The tone of Dilip Nathwani and Peter Davey's article on community based intravenous antibiotic treatment in Britain is unnecessarily negative.[1] We agree, however, that outpatient intravenous antibiotic treatment should be driven by a concern for quality rather than as a cost saving practice. Such therapy was developed in the United States because clinicians wanted to maintain quality care for patients with infections requiring intravenous treatment in the face of pressure from third party payers—such as insurance companies—demanding shorter hospital stays for given diagnoses. The financial savings from home intravenous treatment programmes were shown subsequently. Our programme in Oxford was also developed to promote quality of care rather than to save money. We based it not on an existing home total parenteral nutrition programme but on the realisation that patients with AIDS requiring intravenous treatment for cytomegalovirus retinitis would have a better quality of care if such long term treatment could be provided outside hospital. We expanded this programme to treat other patients with bacterial infections.[2] Our outpatient programme for intravenous antibiotic treatment has allowed patients with serious infections to be given optimal treatment without confining them to hospital for prolonged periods. Our patients are treated in their own homes by district nurses supported by our community liaison nurses and are monitored regularly in our clinic, with 24 hour access to the ward if problems arise.

A useful spin-off from our programme has been a large saving in hospital bed days. In the past five years we have treated 260 patients at home and saved 6033 bed days. Although the value of a hospital bed day varies in different healthcare settings, 80% of our patients are from surgical wards, where prolonged stays have a major impact on waiting list times. Thus earlier discharge with intravenous treatment at home can have major benefits for both patients and purchasers.

We acknowledge, however, that funding issues in the NHS are complex and welcome the call for a nationwide NHS strategy for purchasing outpatient intravenous treatment. This will allow better planning, provide support for hospital and community trusts to set up programmes, and, we hope, regulate the involvement of commercial organisations so that quality of care takes precedence over financial considerations.

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1 Nathwani D, Davey P. Intravenous antimicrobial therapy in the community: underused, inadequately resourced, or irrelevant to health care in Britain? *BMJ* 1996;313:1541-43. (14 December.)
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Macrocytic anaemias

Three fifths of patients with Crohn's disease that has not been operated on have vitamin B_{12} malabsorption

EDITOR—In their article on macrocytic anaemias Victor Hoffbrand and Drew Provan mention rare inherited defects of DNA synthesis and benign familial macrocytosis as causes of macrocytosis,[1] yet they fail to discuss an important cause of malabsorption of vitamin B_{12}—namely, Crohn's disease. It has been estimated that up to three fifths of patients with Crohn's disease that has not been operated on (even those with localised ileal disease or a radiologically normal ileum) have vitamin B_{12} malabsorption.[2] Moreover, since an average district general hospital serving a population of 200 000 will have about 150 patients with Crohn's disease, it is a fairly common cause of B_{12} deficiency. The authors also state that measuring serum gastrin concentrations and taking gastric biopsy specimens may be helpful in investigations of patients with macrocytosis; in routine clinical practice these are of little value. The authors omit to mention IgA antibodies to gliadin. Failure to detect these antibodies is 100% sensitive, specific, and negatively predictive for coeliac disease,[3] a not infrequent cause of folate deficiency and macrocytosis.

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1 Hoffbrand V, Provan D. ABC of clinical haematology. Macrocytic anaemias. *BMJ* 1997;314:430-3. (8 February.)
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Authors' reply

EDITOR—We agree with Roger Barton that tests for serum antibodies to gliadin and endomysium are extremely useful screening tests for enteropathy induced by gluten. We are less certain of the importance of Crohn's disease uncomplicated by an ileal resection or an intestinal stagnant loop as a frequent cause of megaloblastic anaemia due to vitamin B_{12} deficiency.

Our article dealt with macrocytic anaemias, but because of limitations on space we did not detail causes of vitamin B_{12} deficiency, which are only rarely of sufficient severity to lead to megaloblastic anaemia. A large number of conditions exist in which vitamin B_{12} malabsorption occurs and serum vitamin B_{12} concentrations may be subnormal, but these conditions rarely present as macrocytic anaemias due to vitamin B_{12} deficiency. Indeed, enteropathy induced by gluten would be one such example. Our studies of Crohn's disease found that folate deficiency occurred commonly in patients with active disease but that megaloblastic anaemia due to B_{12} deficiency was largely associated with ileal resection or intestinal stagnant loop (both of which were listed in our article as causes of severe vitamin B_{12} deficiency).[1] This experience is also reported by others.[2]

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1 Hoffbrand AV, Stewart JS, Booth CC, Mollin DL. Folate deficiency in Crohn's disease: incidence, pathogenesis, and treatment. *BMJ* 1968;ii:71-5.
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Pancreatic angiography is still valuable preoperatively in insulinoma

EDITOR—The Lesson of the Week by R Perros and colleagues underlines the importance of establishing a firm preoperative—indeed, a pre-imaging—clinical diagnosis in cases of suspected insulinoma.[1] Since the equivocal findings on pancreatic imaging were a factor in this case, we think it important to emphasise that pancreatic angiography is still a valuable preoperative investigation in insulinoma, even if intraoperative ultrasonography is planned. We would make two points not mentioned in the article. Firstly, coeliac angiography alone (if this is really what was performed) would not generally be considered to be adequate in angiographic exploration of the pancreas in such cases. Selective gastroduodenal, splenic, and dorsal pancreatic arteriograms are required to maximise the chances of detecting an insulinoma and to reduce the incidence of false positive findings.[2] Secondly, the discussion makes no mention of hepatic venous sampling after selective pancreatic arterial stimulation. This technique can be performed as a simple extension to the angiography described and is reported as being comparable in sensitivity to portal venous sampling in the detection of insulinoma but with none of its attendant risks.[3] We have avoided portal venous sampling by using hepatic venous sampling after selective pancreatic arterial stimulation (fig 1) and believe that this technique should be used whenever invasive localisation with pancreatic angiography is being performed. In the case in question its use would almost certainly have raised doubts about the clinical diagnosis before surgery was undertaken.

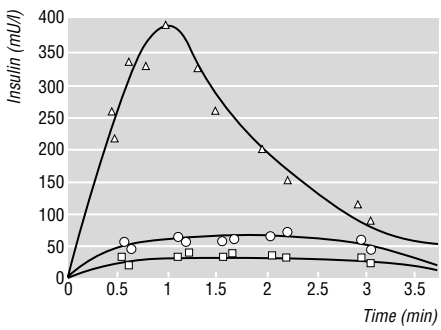

Fig 1 Arterial stimulation-venous sampling in insulinoma of pancreatic tail, showing changing serum insulin concentrations in hepatic vein catheters after calcium injection into each of splenic (△), gastroduodenal (○), and inferior pancreaticoduodenal arteries (×)

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1 Perros P, Henderson AK, Carter DC, Toft AD. Are spontaneous hypoglycaemia, raised plasma insulin and C peptide concentrations, and abnormal pancreatic images enough to diagnose insulinoma? *BMJ* 1997;314: 496-7. (15 February.)
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Public is concerned about gene testing

EDITOR—The decision of the Association of British Insurers that the results of genetic tests should be taken into account when new applications for insurance cover over £100 000 are being considered has created a dilemma for the public.[1] As has been suggested, individuals may opt not to be tested or to choose private testing rather than the NHS. This situation potentially compromises the health of those who are at risk of heritable disease and creates novel uncertainty for those who are not.

In medical research, ethical issues also remain to be resolved. Large scale automated genetic testing is now possible, and the funds available for genetic research will generate considerable activity in the near future. Key questions relate to informed consent and the transfer of DNA samples by researchers to third parties.

We commissioned an opinion poll to examine public attitudes both to insurers' use of genetic tests and to genetic testing in medical research. NOP Research Group carried out a telephone omnibus survey of a nationally representative sample of 1000 adults on 21-23 February this year. Two hundred and eighty respondents said they would not take a genetic test now that they are required to disclose the results to their insurance company. A larger proportion, 358, would object if a tissue sample which they had given anonymously was used in genetic research without their knowledge or consent. Of greater concern, 699 respondents indicated that they would object if their anonymised tissue was sold to a pharmaceutical company without their knowledge or consent.

The results of our poll suggest that we may regret the relative lack of concern over the issue of informed consent in Britain.[2] The Convention on Human Rights and Biomedicine adopted by the Council of Europe last year indicates that samples may be stored and used for purposes other than

those for which they were collected, "in conformity with appropriate consent procedures." Informed commentators take the view that a court would probably regard blanket consent as inappropriate. At present the public is broadly happy to donate samples and to assist medical research in other ways. This willingness to cooperate should be safeguarded with guidelines that provide a clear ethical framework for research in human genetics.

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1 Kmietowicz Z. Health put at risk by insurers' demands for gene test results. *BMJ* 1997;314:625. (1 March.)
2 American Society of Human Genetics. Statement on informed consent for genetic research. *Am J Hum Genet* 1996;59:471-4.

Leukaemia near La Hague nuclear plant

Bias could have been introduced into study

EDITOR—Dominique Pobel and Jean-François Viel found an association between going to the beach more than once a month and leukaemia risk, with an odds ratio of 2.87.[1] Eighty two out of 192 controls were engaged in this activity. If this association were causal, we could expect, roughly, a twofold increase in the incidence of childhood leukaemia in the Nord-Cotentin. Previously, however, the authors had observed an incidence similar to the expected figures (standardised incidence ratio of 1.1),[2] which suggests that a bias could have been introduced in the study design. This issue should be systematically and carefully investigated.

A recall bias could not be ruled out. A selection bias may easily occur since the source population used for identifying controls is ill defined. The control group was identified by the general practitioners who had provided care to the case children. Underlying this design are the tacit assumptions that all the cases were followed by a general practitioner at their time of diagnosis, that those general practitioners are still in practice, and that all the children of the source population were followed by a general practitioner who is still practising. Are these assumptions justified by any evidence? Was the catchment area for these general practitioners identical in 1994-5 (recruitment of controls' parents) and between 1978 and 1993 (recruitment of cases)?

Although the differences are not statistically significant, fathers of cases were ranked in higher social categories than fathers of controls. Some additional criteria would also be useful for comparing cases and controls. For instance, did the controls live farther from the beaches than cases, conditionally on matching? Did they live in similarly sized communities?

To what extent are the variables of interest correlated—mothers' seaside activity during pregnancy, children's seaside activity, consumption of local shellfish, living in a granite house? To what extent are these variables correlated with the distance between the subjects' homes and the beach or with social category or any other characteristic? Numbers allow adjustments, at least when dichotomous variables are used; could the authors show such multivariate analysis?

The authors say they found an excess of childhood leukaemia in the electoral ward containing the reprocessing plant; in a previous paper[2] they reported four cases in this ward from 1978 to 1992 versus 1.4 expected. The four case children played on the beach at least once a month; what about the controls in this ward?

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1 Pobel D, Viel J-F. Case-control study of leukaemia among young people near La Hague nuclear reprocessing plant: the environmental hypothesis revisited. *BMJ* 1996; 314:101-6. (11 January.)
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Study design is questionable

EDITOR—We were surprised by the strength of Dominique Pobel and Jean-François Viel's conclusion that "there is some convincing evidence in childhood leukaemia of a causal role for environmental radiation exposure from recreational activities on beaches."[1]

The study region was restricted to a circle (diameter 35 km) around the La Hague reprocessing plant. Since their original aim was to investigate the apparent increase in incidence of leukaemia in the vicinity of the plant,[2] the design of the study was not ideal for examining recreational activities and food consumption. Cases and controls were tightly matched on geographical region at diagnosis and loosely matched for age. The exposure of interest, parents' recall of their own and their children's dietary and recreational behaviour, may have occurred 30 years or more in the past. Further, there was little information about the control families who refused to participate.

Of the 27 patients ascertained during the 16 year study period, six were young adults (not children) and two had chronic myeloid leukaemia. Given the wide age range, the different diagnostic groups, the small size of the sample, and the multiple tests performed (173 exposure items with one or more methods of testing), we believe that these findings warrant a far more cautious interpretation. Further, the findings rely heavily on tests for trend, which seem predominantly to have been applied even when associations were not statistically significant. The trend statistic is not a traditional epidemiological tool and requires justification under these circumstances. As an example, the figure gives 95% confidence intervals of the relative risk estimates for offspring's recreational activity on local beaches (from Pobel and Viel's table 4). The lower limits are all below 1, and other dose-response relations, other than a positive linear trend, could fit within the range of each estimate.

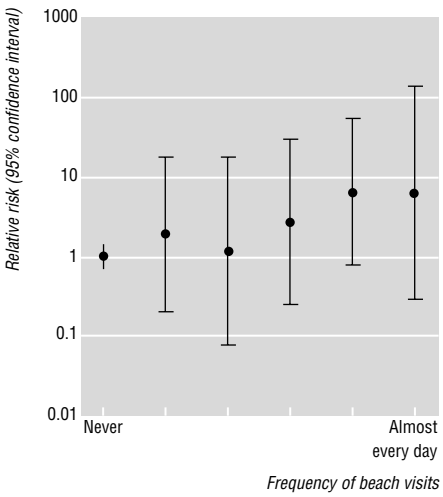

Fig 1 Risk of leukaemia in association with recreational activity on local beaches

Although the possibility that novel pathways of the type proposed should not be discounted,[3] we are not persuaded that Pobel and Viel's study provides convincing evidence one way or the other.

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1 Pobel D, Viel J-F. Case-control study of leukaemia among young people near La Hague nuclear reprocessing plant: the environmental hypothesis revisited. *BMJ* 1997; 314:101-6. (11 January.)
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Scientific context is needed

EDITOR—Dominique Pobel and Jean-François Viel found associations between childhood leukaemia and the use of beaches around the La Hague nuclear fuel reprocessing plant in Normandy by pregnant women and children and the consumption of local seafood by children, which they relate to possible exposure to environmental radioactivity.[1] They do not, however, pay sufficient attention to the scientific context of their results.

In an equivalent case-control study conducted around Sellafield, west Cumbria, Gardner *et al* found no associations between childhood leukaemia and these lifestyle factors when using the appropriate "local" control group, and they drew attention to the "low quality" of data based entirely on questionnaires because of the real (and unquantifiable) possibility of recall bias.[2] This must be particularly so for births over a period of almost 40 years, as in the La Hague study.

Further, Pobel and Viel do not refer to the vast amount of relevant research carried out on environmental radioactivity over the past decade, which has been summarised recently by reports from the National Radiological Protection Board and the Committee on Medical Aspects of Radiation in the Environment (COMARE).[3] COMARE concluded that radiation doses due to discharges are "far too small" to account for the excess of childhood leukaemia near Sellafield. Although Pobel and Viel note the results of the case-control study conducted around Dounreay in Caithness, in which an association between leukaemia and the use of local beaches by children (again based solely on questionnaire data) was also found, they do not refer to the subsequent detailed investigation in the Dounreay area by Watson and Sumner, who carried out a sophisticated programme of measurements of radioactivity in children who had been diagnosed with leukaemia and in unaffected children.[4] They found no indication of unusual levels of radioactivity.

Set against the weak and inconsistent epidemiological evidence for an effect of environmental radioactivity on childhood leukaemia in the vicinity of reprocessing plants is the evidence for the influence of unusual population mixing in these areas, of which Pobel and Viel make no mention. Kinlen has produced compelling evidence from a series of studies for the impact on childhood leukaemia of the mixing of urban and rural populations.[5] Indeed, given this evidence, it would be surprising if the large construction projects at La Hague and at nearby sites had not raised the risk of childhood leukaemia in this area. The potentially important effect of population mixing on the communities surrounding La Hague should at least have been noted.

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1 Pobel D, Viel J-F. Case-control study of leukaemia among young people near La Hague nuclear reprocessing plant: the environmental hypothesis revisited. *BMJ* 1997; 314:101-6. (11 January.)
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Case-control studies have been done in Britain

EDITOR—As authors of a case-control study of leukaemia in children living near nuclear establishments in southern England, we are interested in the case-control study of leukaemia in young people near the La Hague nuclear reprocessing plant.[1] Our study found no links with environmental factors, despite larger numbers and a comprehensive structured questionnaire.[2] In our original report of leukaemia in children age 0-14 years diagnosed between 1972-1985, the excess was most marked in children aged 0-4 years living within 10 km of the nuclear establishments at Aldermaston and Burghfield,[3] where a doubling in risk was found.

Table 1 Incidence of childhood leukaemia in west Berkshire 1972-96 by age and time period (expected numbers are based on leukaemia registration rates in England and Wales)

Age (years)	1972-85[3] Observed	Expected	O/E (95%CI)	1986-96 Observed	Expected	O/E (95%CI)	1972-96 Observed	Expected	O/E (95%CI)
0-4	38	22.3	1.7 (1.2 to 2.3)	27*	17.5	1.5 (1.0 to 2.2)*	65*	39.8	1.6 (1.3 to 2.1)*
5-9	15	13.6	1.1 (0.6 to 1 8)	12†	10.6	1.1 (0.6 to 2.0)	27†	24.2	1.1 (0.7 to 1.7)
10-14	11	9.7	1.1 (0.6 to 2.0)	3	7.6	0.3 (0.1 to 1.2)	14	17.3	0.8 (0.4 to 1.4)
Total	64	45.6	1.4 (1.1 to 1.8)	42*†	35.7	1.2 (0.9 to 1.6)	106*†	81.3	1.3 (1.1 to 1.6)

*Excludes one child residing and treated in the study area who was diagnosed while on holiday elsewhere in England; when the child is included the figures are 1.6 (1.1 to 2.3) and 1.7 (1.3 to 2.1) respectively for 1986-96 and 1972-96.
†Excludes two children: one who was not registered in the national scheme, and one whose initial diagnosis of leukaemia was revised to non-Hodgkin's lymphoma.

Anxieties have been raised again in the local community by media reports of uranium contamination at the former Greenham Common airbase and a newspaper report of increased mortality from childhood leukaemia at Newbury. In view of this we have collated our clinic figures for a further 11 years, giving data for the whole of west Berkshire for 25 years (table 1). The findings for the two periods are similar, although data for 1986-96 may be incomplete since some children resident in the study area may not have been treated at our clinic. There was no increase in the relapse rate or death rate in those with acute lymphoblastic leukaemia, who have been entered into Medical Research Council trials since 1972 (S Richards, personal communication).

Further studies are planned with the Childhood Cancer Research Group, the Oxford Cancer Intelligence Unit, the Newbury Leukaemia Study Group, and the Berkshire Health Authority. We will assess whether the additional and original cases are geographically related to Greenham or the Atomic Weapons Establishments plants and extend the age range studied to 25. It would be interesting to re-examine the incidence of childhood cancer in the same areas of west Berkshire, as a previous report suggests that the incidence of solid tumours is also raised.[4] We hope that some reason or environmental cause can then be postulated.

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1 Pobel D, Viel J-F. Case-control study of leukaemia among young people near the La Hague nuclear reprocessing plant: the environmental hypothesis revisited. *BMJ* 1997; 314:101-106. (11 January.)
2 Roman E, Watson A, Beral V, Buckle S, Bull D, Bauer K, *et al.* Case control study of leukaemia and non-Hodgkins lymphoma among children age 0-4 living in W. Berks. and N. Hants. Health Districts. *BMJ* 1993;306:615-621.
3 Roman E, Beral V, Carpenter L, Watson A, Barton C, Ryder H, *et al.* Childhood leukaemia in the West Berkshire and Basingstoke and North Hampshire District Health Authorities in relation to nuclear establishments in the vicinity. *BMJ* 1987;274:597-602.
4 Committee on Medical Aspects of Radiation in the Environment. *Third report. Report on the incidence of childhood cancer in the West Berkshire and North Hampshire area, in which are situated the Atomic Weapons Research Establishment, Aldermaston, and the Royal Ordnance Factory, Burghfield. (Chairman Professor M Bobrow.)* London: HMSO, 1989.

Deformed insects have been found near nuclear plants

EDITOR—Dominique Pobel and Jean-François Viel's article touches on people's worries about radiation.[1] Before starting to study deformations induced by radiation I worked as a scientific illustrator for the University of Zurich for 25 years, mainly for geneticists and taxonomists, and I had painted leafbugs (Heteroptera) for 15 years in my spare time. Painting mutant fruitflies (Drosophilidae) and normal fruitflies of different families was my main task at the institute and gave me an idea of how nature could look if we go on polluting our environment as we do.

After Chernobyl, I went to contaminated places in Sweden and the Ticino area of Switzerland to look at leafbugs. In summer 1987 I started to collect leafbugs in the areas of Osterfarnebo and Gavle in Sweden and Mendrisiotto in Switzerland, and brought back two pairs of *Drosophila melanogaster*, which I bred in my kitchen as was done in the laboratory. From the first generation I found many deformations of the eyes, antennae, vibrissae, bristles, segments of the abdomen, and wings. The leafbugs were mostly deformed on their antennae, wings, and legs. In Sweden I also found plants with leaf colour changed from green to dark red or changed colour of flowers; I found heavily deformed leaves in Sweden and in the Ticino.

In 1988 I started to collect leafbugs in the main wind directions of the nuclear power plants Gosgen and Leibstadt in Switzerland, where I found the most worrying changes (fig 1). I continued these studies in Sellafield in 1989, Chernobyl in 1990, Three Mile Island in 1992, and Krummel in 1995.

Since 1993 I have been studying leafbugs in the canton of Aargau, Switzerland, which contains four nuclear power plants and one research plant. I collect 65 leafbugs at each of 40 points. The insects with the greatest deformities are found close

CORNELIA HESSE-HONEGGER

Fig 1 Leafbugs found in the grounds of the Paul Scherrer Institute, Villigen, Switzerland, an institute for nuclear research; painted in 1990-1

(5-10 km) to the plants, to the east, southeast, and south; less severe, but frequent, deformations are found southwest of the plants.

In my work, I document not just the quantity but also, by painting the deformed leafbugs, the quality of the deformations. When I have published my work in Switzerland, suggesting that there is a connection between low level radiation from the nuclear plants and the malformations, I have been heavily attacked by scientists.

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1 Pobel D, Viel J-F. Case-control study of leukaemia among young people near La Hague nuclear reprocessing plant: the environmental hypothesis revisited. *BMJ* 1997; 314:101-6. (11 January.)

Author's reply

EDITOR—Jacqueline Clavel and Denis Hémon seem concerned that, as the control selection process relied on general practitioners, there may have been a selection bias. However, the control children were not ill defined, since any parents of a child fulfilling the matching criteria, and not children consulting general practitioners, were asked to join the study. The assumptions about general practitioners' practices are broadly true in this rural area, but I recognise that the stability of catchment areas across time cannot be checked.

Although I have already addressed this issue,[1] they still want to know if the controls live farther from the beaches than cases, but this time conditionally on matching. The results remain non-significant for the closest coast, Vauville beach, and Urville-Nacqueville beach ($P = 0.43$, 0.18, and 0.76, respectively).

Among the four significant exposures (use of local beaches by mothers, use of beaches by children, consumption of local fish by children, and children living in a granitic area), only the first two were significantly correlated ($P < 0.0001$); no other pairwise test yielded significant results among controls ($0.65 > P > 0.24$). In the electoral ward containing the reprocessing plant, all of the four case children played on the beach at least once a month, whereas only 14 of the 33 controls did so ($P = 0.05$). The independent role played by each of the three children's factors is confirmed by a multivariate analysis despite a lack of statistical power on this small dataset (odds ratios: fish consumption = 7.01, $P = 0.05$; beach activity = 2.56, $P = 0.09$; granitic area = 4.15, $P = 0.05$).

Graham Law and Eve Roman have commented on the parents' recall. Exposures may have occurred far in the past and, as in almost every study, some degree of misclassification is inevitable. But the reliability of maternally reported information, in a similar context, has recently been shown to be affected little by time from birth or determination of case-control status.[2] Moreover, media coverage on leukaemia clusters around nuclear facilities had never occurred in France before, nor had a possibility of marine contamination been put forward. Hence, misclassification would be random with regard to case status and should tend to obscure rather than create associations.

Richard Wakeford sets his hopes on the viral hypothesis. Even if a candidate virus is still to be found, and if the British evidence is not so compelling, this is at variance with some French findings.[3]

I hope this additional information will convince the authors that selection or recall biases are unlikely, and that new methods for identifying the environmental pathways are warranted.

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1 Viel J-F. Criticism of study of childhood leukaemia near French nuclear reprocessing plant is unfounded. *BMJ* 1997;314:301.
2 Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy related events: a report from the Children's Cancer Group. *Am J Epidemiol* 1997;145:58-67.
3 Laplanche A, de Vathaire F. Leukaemia mortality in French communes (administrative units) with a large and rapid population increase. *Br J Cancer* 1994;69:110-3.

Advertisements for donepezil (Aricept) in the *BMJ*

Advertisement suggests an unrealistic improvement in mental status

EDITOR—I wish to express my anger and concern that advertising space on the wrapper around the clinical research edition of the *BMJ* (issues of 3 and 10 May) was sold to promote donepezil hydrochloride (Aricept). This is the first time that I have been aware of a promotion of this nature, and I find this form of advertising disturbing. While I appreciate that the *BMJ* generates necessary income from pharmaceutical companies and I can deal with advertisements within the journal, I find that to be faced by a paper strip on top of the *BMJ* that has to be forcefully removed before one can even read the contents page is irritating and intrusive. No doubt because of this, it is a successful marketing ploy and generates enormous amounts of income. As a general policy, however, I hope that the journal will reconsider accepting this type of advertisement, as I am sure I am not alone in finding it offensive.

The *BMJ* has taken great strides in supporting a critical and rational use of the evidence base in medicine. What policy is adopted in scrutinising the content of advertisements placed in the *BMJ*? The promotion for donepezil—"Mum has Alzheimer's but she knew I was calling today" and the related photographs—implies that in patients with Alzheimer's disease treatment with the drug will improve function enough to have a measurable impact on the carer's mood. As far I am aware there has been one published randomised controlled trial of the use of donepezil in Alzheimer's disease, and this showed no improvement in the quality of life of carers.[1] The advertisement suggests an unrealistic improvement in the mental status of patients.

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1 Rogers SL, Friedhoff LT and Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of the US multicentre randomised, double-blind, placebo-controlled trial. *Dementia* 1996;7:293-303.

Local committee has declined to approve NHS hospital prescription of donepezil

EDITOR—The fact that the *BMJ* of 10 May carried an external binder, a full page advertisement, and an insert summary for the product characteristics of donepezil hydrochloride (Aricept), the recently launched drug for Alzheimer's disease, spoilt my weekend.

I am a singlehanded psychogeriatrician serving a population of 30 000 patients aged over 65 years, spread over 2124 km^2. I am not alone among my colleagues in having just about kept my head above water (with a catchment population over twice that recommended by the old age section of the Royal College of Psychiatrists) until now, when the rising tide has finally broken the defences. My referral rate for the assessment of patients aged over 65 with presumed organic mental disorder has soared, my re-referral rate is soaring too, and so are queries about donepezil from patients, relatives, carers, general practitioners, community psychiatric nurses, and other consultants. My waiting time for first outpatient appointments has increased from seven to 10 weeks and will soon break the standard in my local patient's charter (12 weeks).

My local health authority has just refused my trust the final £20 000 needed to fund a sorely needed additional consultant in adult psychiatry. Thus I cannot very well hand all elderly patients with functional problems over to my colleagues in order to

concentrate on patients with organic problems. My local drugs and therapeutics committee has just followed the health authority's directive and declined to approve the NHS hospital prescription of donepezil. None of the local fundholding general practitioners to whom I have spoken, who have patients who could benefit from this drug, are prepared to pay the estimated £1000 a year for it.

I shall be writing three private prescriptions for donepezil this week, thinking of the 80 or so patients in Herefordshire who might benefit from the drug and all those patients and carers who would be better served by at least two of me.

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✾The *BMJ* carries advertising to provide financial support to the journal and information to readers. Advertising must be immediately recognisable as such, and we never sell advertising linked to editorial material (unlike many medical newspapers). All advertisements are approved by the editorial team, but as European and British legislation governs pharmaceutical advertising we rarely reject advertisements on the grounds of unsubstantiated or misleading claims. We sometimes reject advertising because we think that readers will find it offensive, but generally our policy is liberal. Readers are well able to tell the difference between advertising and editorial material. Donepezil hydrochloride has received a product licence, and the manufacturer naturally wants to promote it.

We monitor all complaints from readers, and this is the first we have received about advertising wrappers despite their having been used intermittently for two years. The wrappers don't seem to offend many readers.—EDITOR.

Editorial should have mentioned National Sports Medicine Institute of the UK

EDITOR—Mark E Batt and Donald A D Macleod's editorial about sports medicine outlined the needs of and approach required for the development of sport and exercise medicine in Britain.[1] I was disappointed, though, that there was no mention or recognition of the role and work of the National Sports Medicine Institute of the United Kingdom. This is especially so as both authors are current members of the management committee. I appreciate that many people and organisations have laboured towards the recognition of sport and exercise medicine, but the role of the institute and especially its past chairman, Ossie Wheatley, who chaired the working party, deserves some mention.

The institute was set up to be an umbrella organisation that would facilitate the development of the medical care of sports people at all levels. We have consistently advocated regulated training and examination under the auspices of the royal colleges with a view to the establishment of sport and exercise medicine as a recognised specialty. Sport needs a structured delivery of care, which cannot exist without such control and recognition. We look forward to the formation of the board of sport and exercise medicine by the Academy of Royal Colleges as it is only through the royal colleges that appropriate development can be achieved. The role of the National Sports Medicine Institute of the United Kingdom is still evolving. It is up to those on the management committee to ensure that the institute serves both sport and the profession and becomes the single respected voice for its member organisations, which include the royal colleges and the British Association of Sport and Medicine.

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1 Batt ME, Macleod DAD. The coming of age of sports medicine. *BMJ* 1997;314:621. (1 March.)

Cancellation of debt of poorest people would be worthy memorial to millennium

EDITOR—Andrew Haines and Richard Smith rightly argue that the increasing disparity in wealth, between and within countries, is having such a profound effect on health that doctors must cooperate with others to analyse the "pathology" of poverty and lobby for change.[1] Medical Action for Global Security, the British affiliate of International Physicians for the Prevention of Nuclear War, is doing just that. By linking with health professionals globally and by working with economists, we are examining why health gains are being eroded in parts of the world.

Of the many obstacles to reducing poverty, debt repayment is among the most formidable. By the end of the decade more than half of sub-Saharan Africa's population—300 million people—will be living in poverty; sub-Saharan Africa is the only region of the world where malnutrition is rising. Nevertheless, the region struggles to service a debt that has reached two and a half times its annual export earnings.[2] Four times more is spent on servicing debt than on health. Far from being the caricatured "basket cases," many African countries had successful primary health care in the 1970s and impressive achievements in literacy, child mortality, and life expectancy.[3] But throughout the 1980s these achievements were eroded as money was diverted from social spending to debt servicing. By 1990 many African countries were spending less per capita on health than they had done in 1980.

It is ironic that the World Bank, which is the main source of funding for health (total annual health lending roughly $3bn[4]), is also the organisation responsible for some of this deterioration. With the shift in emphasis from state provision to privatisation and "cost recovery" poor people have been asked to pay for health and education, which they cannot afford. The bank's policies are so driven by monetarist ideology that the living standards of millions take second place to chasing some economic nirvana. Is it right that a bank should dictate global health strategy to such an extent?

I suggest that health professionals could adopt the idea of a jubilee for 2000: a one off cancellation of the unpayable debt of the poorest people, in countries where health as a basic right has been revoked. Surely it would be a worthier memorial to the millennium than the construction of a Ferris wheel in London.

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1 Haines A, Smith R. Working together to reduce poverty's damage. *BMJ* 1997;314:529-30. (22 February.)
2 Pettifor A. *A fresh start for Africa.* London: Christian Aid, 1996. (Debt Crisis Network working paper.)
3 United Nations Development Programme. *The human development report 1991.* New York: Oxford University Press, 1991.
4 The World Bank, listening and learning [editorial]. *Lancet* 1996;347:411.

Nurses are right not to take on responsibilities for which they have not been properly prepared

EDITOR—I write in response to the letter from J C Hughes about the need for nurses to accept more responsibility and for doctors to receive better training in the care of terminally ill patients.[1] I agree with much that Hughes says, but it is important to put the record straight about the "rules" of the United Kingdom Central Council for Nursing, Midwifery and Health Visiting.

Hughes states that "nurses do not have to do anything they do not feel competent to do." This is not, as Hughes reports, an edict from the central council to the effect that individuals should renege on their proper and appropriate professional responsibilities. Indeed, it is just the opposite. The intent, as would be expected with any responsible professional organisation, is to ensure that nurses do not take on roles and responsibilities for which they have not been properly prepared and that might be to the detriment of patients' and clients' safety. Surely all health care professionals would agree with this position.

All those on our register (about 650 000) have a personal professional accountability for their actions and can therefore be called to account for all that they undertake. It would be irresponsible in the extreme were they to take on additional activity merely because they had been told or asked to do so by others.

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1 Hughes JC. Doctors, nurses, and terminal care. *BMJ* 1997;314:306. (25 January.)