Non-immunocompromised patients with invasive aspergillosis

Patient	Sex	Age	Clinical details
1	M	60	Multisystem failure following aortobifemoral grafts for peripheral vascular disease
2	F	53	Chronic rheumatic aortic and mitral valve disease; acute renal failure due to vasculitic-type glomerulonephritis
3	M	74	Panlobular emphysema and postmortem evidence of 1-antitrypsin deficiency

categories (table).[2] None of these patients was neutropenic during their hospital stay and none was diagnosed before necropsy as having invasive aspergillosis. Unlike the cases of Dr Hovenden and colleagues, two showed widely disseminated disease, indicating that systemic spread may also occur in such patients.

I agree with Dr Hovenden and colleagues in most respects and particularly welcome their emphasis on the importance of taking aspergillus isolates seriously in any patient with progressive pulmonary infiltrates. My research has shown, however, that several of their comments require some qualification. While it is true that profound neutropenia is common in many cases of invasive aspergillosis, this was a feature in only two out of 12 liver transplant patients with aspergillosis.[2] We have previously shown that a more important risk factor in this group is the use of high dose steroids to prevent rejection.[3] Furthermore, in our series there was no significant association between the presence of neutropenia and the incidence of systemic spread. In contrast, there was a highly significant association with use of high dose corticosteroids.

Finally, the association between aspergillus and building work may have been overemphasised. Despite the presence of a substantial building project on the hospital site, the source of infection in our liver transplant patients at the Queen Elizabeth Hospital, Birmingham, was eventually traced to a contaminated air shaft (T Elliot, personal communication).

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1 Hovenden JL, Nicklason F, Barnes RA. Invasive pulmonary aspergillosis in non-immunocompromised patients. *BMJ* 1991;**302**:583-4. (9 March.)
2 Boon AP, O'Brien D, Adams DH. A ten year review of invasive aspergillosis detected at necropsy. *J Clin Pathol* (in press).
3 Boon AP, Adams DH, Buckels J, McMaster P. Cerebral aspergillosis in liver transplantation. *J Clin Pathol* 1990;**43**: 114-8.

Radiation workers and childhood leukaemia

SIR,—One thing that emerges from the article by Mr James Urquhart and colleagues is that neither paternal employment nor occupational radiation exposure at Dounreay can apparently explain the excess of childhood leukaemia within the Caithness area.[1] Because of the relations found earlier for Sellafield in West Cumbria,[2] however, the following comments are relevant.

Annual average doses of external ionising radiation among workers in the nuclear industry have fallen over the years. For example, mean annual doses to radiation workers at Sellafield decreased from around 15 mSv during the 1950s to around 5 mSv during the 1980s.[3,4] At Dounreay, which became operational later than Sellafield, overall doses have been lower—thus 13% of Dounreay radiation workers had accumulated over 100 mSv to 1979 (mean 47 mSv)[5] compared with 34% of Sellafield workers to 1983 (mean 124 mSv).[3] The results presented by Urquhart and coworkers therefore relate to a lower exposure working environment, and as they are based on a smaller study, as the authors say, they do not contradict the earlier findings.

For comparison, results from the studies in the Dounreay and Sellafield areas for workers at the nuclear installations only and their children are shown in the table, with non-Hodgkin's lymphoma included as it is not possible to separate leukaemia cases in the former paper.[1] If the Sellafield figures are proportionally scaled down to the size of the Dounreay study then little major difference is seen on the small numbers involved.

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1 Urquhart JD, Black RJ, Muirhead MJ, *et al.* Results of a case-control study of leukaemia and non-Hodgkin's lymphoma in children in Caithness near the Dounreay nuclear installation. *BMJ* 1991;**302**:687-92. (23 March.) [And see correction, *BMJ* 1991;**302**:818. (6 April.)]
2 Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *BMJ* 1990;**300**:423-9.
3 Smith PG, Douglas AJ. Mortality of workers at the Sellafield plant of British Nuclear Fuels. *BMJ* 1986;**293**:845-54.
4 BNFL Health and Safety Directorate. *Annual report on occupational safety 1989.* Risley: British Nuclear Fuels, 1990.
5 Beral V, Inskip H, Fraser P, Booth M, Coleman D, Rose G. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946-1979. *BMJ* 1985;**291**:440-7.

Preventing fraud

SIR,—Ms Jane Smith seems to concentrate on the teaching of research ethics and reduction of the need for publication to reduce fraud, asking for retention of data to help in investigation, thus seeming to say that prevention and investigation are important.[1] Detection of fraud, however, is not considered.

In this regard the advent of good clinical practice should play a part. Its elements are laid down in many documents and laws from the American Food and Drugs Administration[2] and are now brought to Europe by the guidelines issued by the Committee for Proprietary Medicinal Products.[3] The major tenets of good clinical practice are to assure the protection of the research subject and to confirm the integrity of the data.

At present good clinical practice relates only to the development of pharmaceuticals and medical devices. The job of assuring the validity of the data lies initially with the investigator and with monitors, who, among other obligations, have to validate data by comparing the research data written into case report forms with source documents such as patient and physician records and other sources of raw data such as laboratory and test reports.

Pharmaceutical companies that work to good clinical practice must then have at least one tier of auditors to audit the work of both monitor and investigator. In the United States further assurance of the data is provided by the Food and Drugs Administration, which has a large team of compliance officers to check data validity. It is this typically American attitude of checks and balances that maximises the chance of detecting fraud in American pharmaceutical research. The Food and Drugs Administration publishes a blacklist of investigators who have fallen foul of the audit. It also has the ability to bring criminal charges against investigators perpetrating fraud.

Our company has been operating to good clinical practice in the United Kingdom for several years, and we have strongly suspected fraud on several occasions. It is likely that the advent of good clinical practice in Britain and Europe will increase the detection of fraud. The long term effect should be to reduce the frequency of its occurrence.

At present in the United Kingdom, if fraud is detected in pharmaceutical research the only action available is to report the matter to the General Medical Council. Europe does not yet have specific laws on the subject. No government yet undertakes quality audits, with the exception of Greece, which has two auditors. Indeed, the only other country intending to audit is France, which has trained 10 auditors. These, however, have yet to undertake a definitive audit.

All these schemes may help detect fraud in pharmaceutical research, but they do not do anything to increase the detection of fraud in academic research. It is surely not enough to make fraud less likely to occur, nor enough to investigate it once suspicions arise and allegations are made. We contend that academic institutions should set up procedures for auditing research under their jurisdiction in parallel with the developments in the pharmaceutical industry.

The pharmaceutical industry seems to be doing so much to detect fraud, but many academics are still more suspicious of research sponsored by companies than they are of work sponsored from outside the industry. Perhaps academic and professional bodies have something to learn from the experience of the pharmaceutical industry regarding good clinical practice and assuring the validity and integrity of data.

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1 Smith J. Preventing fraud. *BMJ* 1991;**302**:362-3. (16 February.)
2 United States Code of Federal Regulations. Title 21:Sections 50, 56 and 312.
3 CPMP Working Party on Efficacy of Medicinal Products. *Note for guidance: good clinical practice for trials on medicinal products in the European community.* Brussels: Commission of the European Communities, 1990.

Father's external radiation dose (mSv) before conception of child for leukaemia and non-Hodgkin's lymphoma cases and controls born to Dounreay and Sellafield workers

Nuclear installation	Child*	Total preconception dose		6 Months preconception dose	
		<100 mSv	≥100 mSv	<10 mSv	≥10 mSv
Dounreay	Case	3	0	2	1
	Control	14	1	14	1
Sellafield	Case	7	4	6	4
	Area control	42	5	31	8
	Local control	59	3	46	5

*See Gardner *et al* for definition of area and local controls (some children could be both). Area controls are more comparable with the controls selected by Urquhart *et al*.[1]

Confidence intervals and sample sizes

SIR,—Dr Leslie E Daly has argued that it is important to estimate appropriate sample sizes and that sample sizes based on the width of confidence intervals can result in studies too small to achieve meaningful results.[1] He suggests that calculations for sample sizes based on confidence intervals should specify the confidence level, the minimum size of the comparative measure that we wish to estimate unambiguously, and the chance of achieving this if the measure actually had this minimum value (power).

We fear that consideration merely of statistical factors in estimating sample sizes conveys a false respectable rigour, which is misleading. All the