similar to ticlopidine, which is known to have severe adverse effects on blood cells.[2] Nevertheless, a loss of taste has not been described in patients given ticlopidine.[2–5]

A 76-year-old woman with transient vertebrobasilar ischaemia was given clopidogrel, 75 mg daily, because she had mild gastric disorders when treated with aspirin, 300 mg daily. She had a history of mammary carcinoma (1979) without radiotherapy or chemotherapy, sarcoidosis (1982), and a hyperfunctioning thyroid adenoma that was surgically removed (1983). After discontinuation of aspirin treatment the gastric disorders disappeared. About 6 weeks after the start of the clopidogrel treatment the patient observed a loss of taste. Smell was not impaired. Findings of cranial computed tomography, routine laboratory tests, and electroencephalogram were normal. 3 weeks after the taste loss was observed, clopidogrel treatment was discontinued. 20 days later, the patient recognised the taste of red and white currants. Within a few days, there was full recovery of taste.

A 64-year-old man with transient cerebral ischaemia who was receiving aspirin treatment (300 mg daily) had been given clopidogrel, 75 mg daily for 2 months, when loss of taste was observed. Smell was not impaired. The clopidogrel treatment was stopped and aspirin was resumed. Full recovery of the loss of taste was observed within 6 weeks, but another transient cerebral ischaemic attack occurred. Therefore, the clopidogrel treatment was resumed but with a different preparation (Iscover, Bristol-Myers Squibb, München, Germany, rather than Plavix, Sanofi Winthrop, München, Germany). About 2 weeks later, the patient again reported a loss of taste. Therefore, the treatment was discontinued again. 6 weeks later the loss of taste persisted.

Several mechanisms could lead to ageusia.[3] Information from the manufacturer suggests that ticlopidine and clopidogrel are metabolised in the thiophene ring, which includes ring opening. The active metabolite of clopidogrel has a carboxylic group and a sulphhydryl group as a result of ring opening. In contrast, the active metabolite of ticlopidine has not been reported. Detailed information about metabolites of the two drugs is not available. Therefore, we cannot draw conclusions about the mechanistic background of this rare adverse effect.

In addition to the two cases we describe, only one unpublished case has been reported to the German regulatory authorities.

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Risk of cryptogenic fibrosing alveolitis in metal workers

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We report increased proportional mortality from cryptogenic fibrosing alveolitis in the workforce of a major UK engineering company. Measures of metal exposure from unbiased historical occupational records showed that among employees who have worked with metal, the risk of death from or with cryptogenic fibrosing alveolitis increased in relation to the duration of metal-working.

Retrospective case-control studies suggest that the risk of cryptogenic fibrosing alveolitis (CFA) may be greater in people who have worked with metal or wood.[1–3] To exclude the possibility that these findings have arisen from biased recall of occupational exposure, we estimated proportional mortality and the relation between death from or with CFA and metal-work exposure, by the use of unbiased archived occupational histories and pension-fund mortality data from the workforce of a major UK engineering employer.

Participants were identified from death certificates held in pension-fund records of employees working for Rolls-Royce Plc at UK sites in Derby, Coventry, Newcastle, East Kilbride, and Bristol. Cases of CFA were defined as those in which the terms cryptogenic fibrosing alveolitis, fibrosing alveolitis, or idiopathic pulmonary fibrosis were recorded anywhere on the death certificate. A random sample of controls was selected at a ratio of about ten controls per case, from deaths with no mention of fibrotic lung disease. We estimated the proportional mortality ratio (PMR) for death from or with CFA in this cohort by indirect standardisation for age and sex relative to national all-mention mortality data for 1986,[4] the second of only 2 years for which all-mention mortality data were provided for England and Wales and the year closest to the median age at death of our cohort. To estimate indirectly whether the prevalence of smoking in our cohort was likely to be higher than the national average we also calculated the cohort PMR for lung cancer. Lifetime occupational data were obtained from individual employment records held by the company for each employee, and each job was coded according to whether it involved work with metal, by a Rolls-Royce occupational hygienist who was not aware of case or control status. The effect of ever having worked with metal on the risk of death from or with CFA was then estimated by logistic regression with adjustment for sex and age at death and analysed in relation to duration of exposure among the population of exposed cases and controls. We then carried out posthoc subgroup analyses to examine the effect of specific metal-working occupations and individual metal exposures. All analyses used STATA (version 5).

We identified 20 526 death certificates in the pension-fund archive, documenting deaths occurring between 1967 and 1997 (table 1). Median age at death was 71 years (range

	Years available	Total deaths	CFA deaths	CFA deaths per 1000	Occupational records located for cases	Number of controls selected	Occupational records located for controls
Site							
Derby	1969–95	4911	16	3·3	13 (81%)	156	123 (79%)
East Kilbride	1968–97	4979	5	1·0	1 (20%)	141	53 (36%)
Bristol	1973–95	3977	17	4·3	7 (41%)	124	49 (40%)
Newcastle	1967–93	3834	10	2·6	1 (10%)	109	11 (10%)
Coventry	1973–95	2825	7	2·5	0	91	0
Total	··	20 526	55	2·7	22 (40%)	621	236 (38%)

Table 1: **Analysis of death certificates and occupational records**

Occupation	Cases (n=13)	Controls (n=125)	Odds ratio (95% CI)
Engineers	1 (5%)	6 (3%)	1·76 (0·19–16·5)
Furnace men	1 (5%)	20 (8%)	0·51 (0·06–4·23)
Machinists	5 (23%)	73 (31%)	0·72 (0·23–2·27)
Toolmakers	0	2 (1%)	
Fitters	2 (9%)	24 (10%)	0·93 (0·19–4·68)
Electricians	1 (5%)	2 (1%)	5·50 (0·38–79·9)
Sheet-metal workers	4 (18%)	2 (1%)	21·0 (3·47–141·9)
Welders	0	5 (2%)	
Coach builders	0	14 (6%)	

Table 2: **Breakdown of jobs involving metal exposure listed in lifetime occupational records**

17–102) and median year of death 1988. 86% were male. There were 100 deaths for which any fibrotic lung disease was mentioned on the certificate, of which 55 (93% male, 2·7 per 1000 of the cohort) met our case definition for death from or with CFA. This number was significantly greater than the estimated 39·5 (1·9 per 1000) deaths from or with CFA expected in the cohort from national mortality rates. The PMR for death from or with CFA in the Rolls-Royce workforce was 1·39 (95% CI 1·07–1·82; p=0·02). The PMR for lung cancer was not increased (0·97 [0·93–1·02], p=0·2).

We were able to locate occupational records for 22 (40%) cases and 236 (38%) controls; the remaining records (including all those at one site) had been lost or destroyed. The median ages at death for these cases and controls were 68 and 69 years, and the median years of death 1987 and 1988, respectively. There were 13 (59%) cases who had worked with metal compared with 125 (53%) controls (odds ratio adjusted for age and sex 1·08 [0·44–2·65], p=0·9). The median duration of work with metal in cases was 9·3 years (IQR 5·7–20·2) and 5·4 years (2·4–14·4) in controls. Among employees exposed to metals there was a direct relation between duration of exposure and the risk of CFA (odds ratio per 10 years of exposure 1·71 [95% CI 1·09–2·68]; p=0·02). There was no evidence of an association between duration of employment and CFA for Rolls-Royce employees who were not metal-workers. The analysis of specific job titles involved subgroups of very small numbers but cases were more likely to have been sheet-metal workers (table 2). There was also a non-significant increase in risk associated with having worked with lead, cadmium, or silver.

The risk of death from or with CFA in this cohort was low, but significantly higher than expected from national mortality data. This finding is unlikely to be due to confounding by cigarette smoking, since proportional mortality for lung cancer in the cohort was not increased. Although in qualitative terms there was no significant increase in the risk of death from or with CFA associated with metal-work exposure, the 95% CI for the qualitative odds ratio estimate were broad and included those reported previously.[2,3] We did not find any significant association between CFA and individual metal exposures, but there was a non-significant association with lead exposure, which is consistent with our findings in a previous study.[3] The increased risk of CFA in sheet metal workers suggests that this occupation in particular needs further investigation.

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Hirudin treatment in a breastfeeding woman

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We report on a breastfeeding woman with deep venous thrombosis treated with hirudin because of heparin-induced thrombocytopenia, in whom hirudin was not detectable in human breastmilk.

Hirudin is a direct thrombin inhibitor, recommended for anticoagulation of patients with acute coronary syndromes[1,2] and the immunological type of heparin-induced thrombocytopenia (HIT).[3] The safety of hirudin in pregnancy and during breastfeeding has not been investigated.

A 34-year-old breastfeeding woman (weight 50 kg, height 168 cm) developed a deep vein thrombosis in her calf 7 weeks after delivery and was treated with low-molecular-weight heparin (LMWH) subcutaneously (2×5000 U Fragmin P forte, Pharmacia & Upjohn, Erlangen, Germany). On day 20 of heparin treatment, her platelet count decreased from 352 000/μL to 239 000/μL and repeated heparin-PF4-antibody-assays (ELISA) were positive, indicating HIT. LMWH treatment was discontinued and 50 mg lepirudin twice daily (Refludan, Hoechst Marion Roussel, Bad Soden, Germany) was given subcutaneously. Plasma hirudin concentrations were 0·5–1·0 mg/L 3 h after injection. Because she wanted to continue breastfeeding, hirudin was measured in breast-milk 3 h after subcutaneous hirudin administration. Measurement was by use of a chromogenic substrate assay, developed to measure hirudin in plasma.[4] To separate the fat from the breastmilk before measurement, 100 μL hydrochloric acid was added to 2 mL breastmilk, the mixture was heated at 56°C for 15 min then centrifuged three times for 20 min each at 2000 g.

The test was calibrated with an untreated volunteer's breastmilk, to which hirudin in concentrations of 0–1·5 mg/L were added before separation of fat. The lower detection limit was 0·1 mg/L. After subcutaneous lepirudin administration 50 mg twice daily, no hirudin could be detected in breastmilk of the nursing mother, although her plasma hirudin level was within the therapeutic range (0·73 mg/L). Breastfeeding was continued during the period of hirudin treatment for 3 months. Platelet counts reached baseline values 6 days after discontinuation of LMWH. The heparin-PF4-antibody assay titres decreased at the same time, and the test result became negative 6 days after discontinuation of LMWH. Neither thromboembolic nor bleeding events occurred in mother or infant.

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