electrical nerve stimulation for at least one month. None had been helped by diet or drug treatment.

A physiotherapist explained the nature of transcutaneous nerve stimulation and assessed the intensity of pain using a visual analogue scale.³ Transcutaneous nerve stimulation was given using a Neen system 7737 stimulator (Neen Pain Management Systems, Swanton Morley, Dereham, Norfolk), which delivered an electrical stimulus of 9 V, frequency 30-100 Hz, pulse width 200 μ s. The stimulating electrodes were initially placed over the site of the pain, but if this produced no effect other positions were tried, either paraspinal over the dorsal root of the affected dermatome or on the appropriate acupuncture sites. After an instruction period of one hour the patients were lent a machine to assess its benefit over one month. During this time they were seen at two and four weeks, when further assessments of pain severity were made. Changes in pain intensity were calculated as the percentage alteration in the visual analogue score from the original reading³ and the patients divided into three groups: no response (<33% reduction), moderate response (33-66% reduction), and good response (>66% reduction).² Eight patients with no response stopped treatment within the first four weeks; the remainder were followed up for at least six months (maximum 11 months).

The initial mean values on the visual analogue scale were the same in the three groups whatever the response (8.7, 8.7, and 9.2 respectively). Twenty one patients reported benefit from the treatment at one month, and 15 of these continued the treatment for at least six months (table). At six months 10 reported a good response and five a moderate response. The effective sites of electrode placement in those who initially responded (n=21) were over the site of pain in 17, paraspinal in five, and at the acupuncture points in two; three patients responded at more than one site. In those who continued treatment the mean pain score on the visual analogue scale at six months was 4.1 in those with a moderate response and 1.4 in those with a good response. The six people who discontinued treatment between one and six months did so either because of a loss of effect (four cases) or because they were unable to afford a machine (two cases).

Numbers of patients with functional abdominal pain responding to transcutaneous nerve stimulation at one, three, and six months

	Follow up (months)		
	1	3	6
Good response	15	13	10
Moderate response	6	6	5
Stopped treatment	8	10	14
Total	29	29	29

Comment

Severe functional abdominal pain is often difficult to treat. The results of this open trial show that transcutaneous electrical nerve stimulation may provide relief from this condition over at least six months. The treatment is acceptable to the patients (15 bought their own machines) and is harmless.

We accept that the pain reduction seen in these patients may have been placebo response but we doubt that this is the whole explanation. A placebo response to any treatment in functional abdominal pain may initially be as high as 70%, but this response is rarely maintained for more than two months.⁴ Unfortunately, it is difficult to undertake a blinded trial of transcutaneous electrical nerve stimulation because of the associated tingling. Attempts have been made in the laboratory to compare transcutaneous nerve stimulation with a supposed subthreshold electrical stimulation reinforced by a visual wave seen on an oscillograph,⁵ but this technique did not seem appropriate for our study. Whatever the mechanism we conclude that transcutaneous nerve stimulation may help some patients with functional abdominal pain unresponsive to drugs.

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Cigarette smoking and prolactin in women

Recent reports have shown that cigarette smoking may be associated with low prolactin concentrations in premenopausal women.¹ Although this has been confirmed experimentally in rats,^{1,2} there has been no investigation in postmenopausal or younger women in the general population. We present an analysis of cigarette smoking and prolactin concentrations in a large group of healthy premenopausal and postmenopausal women.

Methods and results

All data were from the third phase of the Guernsey study, a prospective investigation of hormones and risk of breast cancer. Over 5000 women aged 30 or over and living on Guernsey volunteered to provide blood and urine specimens and complete a health questionnaire. Although a history of cigarette smoking was not routinely gathered, the first 732 subjects were questioned about their smoking habits for another study.

Blood samples were drawn between 1300 and 1930 hours, and serum was frozen at -20°C. Prolactin was measured using the method of Kwa and Wang (normal concentration ≤ 1.2 nmol/l (30 μ g/l)).³ Women who had menstruated in the six months previously were considered premenopausal; all others were considered postmenopausal. Women who had had a hysterectomy (with or without oophorectomy) formed a separate group for analysis. Women taking drugs that alter the concentration of prolactin (phenothiazines, reserpine, methyl dopa, tricyclic antidepressants, metaclopramide, oral contraceptives, and oestrogens) were excluded from analysis, as were those for whom drug information was incomplete.

Because of the skewed distribution of prolactin measurements geometric means were used to summarise the data, and analysis of covariance was performed on log transformed values to assess the impact of various factors.

After exclusions for missing data and drugs 508 subjects remained for analysis. The table summarises geometric mean prolactin concentrations by smoking and menopausal state. In both smoking and non-smoking groups premenopausal women had higher prolactin concentrations than postmenopausal women.

Subject details and geometric mean prolactin concentrations

	Smokers*	Non-smokers*
Mean (SD) age (years)	47.6 (8.8)	48.7 (9.2)
Mean (SD) weight (kg)	64.0 (10.9)	64.5 (10.0)
Mean (SD) parity	2.4 (1.6)	2.2 (1.3)
Mean (SD) hour of blood draw	1649 (113 min)	1646 (109 min)
Geometric mean prolactin (nmol/l):		
Premenopausal women (No)	0.38 (60)	0.44 (213)
Naturally menopausal women (No)	0.29 (33)	0.32 (119)
Surgically menopausal women (No)	0.24 (11)	0.34 (70)

*Excluding women taking prolactin altering drugs.

Conversion: SI to traditional units—Prolactin: 1 nmol/l=0.04 μ g/l.

Conversely, within both the premenopausal and postmenopausal groups women who smoked had lower prolactin concentrations than non-smokers. Analysis of covariance showed that after control for age and weight, menopausal state and smoking were highly significant ($p<0.01$). There was no support for variation in the smoking effect by menopausal state, as the interaction between these two variables was not significant.

Comment

The differences we found were unlikely to have been due to intake of drugs because of the strict inclusion criteria used. Age and weight were considered as covariates and could not explain these effects. Meals may alter prolactin concentrations, but there was no indication that the subjects who smoked differed from non-smokers in the time their blood was taken.

Our results agree with previous findings that smoking or parenteral nicotine is associated with low prolactin concentrations.^{1,2} Some studies using human subjects found smoking to be associated with increased prolactin concentrations but these assessed acute changes after smoking.⁴ All studies, like ours, that compared long term smokers with long term non-smokers have found lower concentrations among smokers. A similar distinction between short term and longer term effects has been found in rats.⁵

As dopamine inhibits prolactin secretion our results suggest that smoking has a clinically important dopaminergic influence in the central nervous system. The negative association between Parkinson's disease and smoking is consistent with this view.¹ Indeed, experiments with rodents have confirmed that cigarette smoke increases dopamine turnover in the central nervous system.² Because dopamine may inhibit secretion of luteinising

hormone this may help to explain the association of cigarette smoking with various menstrual disorders, including an early menopause.² Thus smoking may have hormonal effects due, at least partly, to an increased release of dopamine.

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Leucocytoclastic vasculitis and pneumonitis induced by metformin

We present what is to the best of our knowledge the first reported case of vasculitis and pneumonitis induced by metformin.

Case report

A 59 year old woman was admitted to the department of dermatology because of a purpuric eruption on her legs, thighs, buttocks, forearms, and lower abdomen that had started two weeks previously. During this period the patient had also experienced arthralgia of the ankles without fever. For the past five years she had been treated for non-insulin-dependent diabetes mellitus with glibenclamide, 10 mg/day. Four months before admission she had also been given metformin, 2.55 g/day.

On admission the patient was in good general condition; her blood pressure was 130/80 mm Hg, she had a pulse rate of 82 beats/min, and a temperature of 36.5°C. Slightly indurated purpuric papules were seen on the lower abdomen, thighs, forearms, buttocks, and legs. Some of those on the legs had delicate haemorrhagic vesicles in the centre. Other findings included an apical systolic murmur with normal pulses and a mild, painful swelling of the ankles. Chest radiography showed bilateral basilar pulmonary infiltrates. Specimens taken by punch biopsy of a purpuric papule from the thigh showed an intense perivascular polymorphonuclear infiltrate, fibrinoid deposits in the small dermal vessels, and fragmented neutrophils (nuclear "dust") consistent with leucocytoclastic vasculitis.¹ Direct immunofluorescence did not show evidence of immune deposits of IgM, IgG, or C3. Glibenclamide and metformin were discontinued and replaced with injections of insulin. Prednisone 0.5 mg/kg/day was given orally and rapidly tapered according to her clinical condition. Repeated chest radiography 10 days after beginning treatment showed a clear diminution in the size of the lung infiltrates. The patient was discharged after four weeks and prescribed 20 mg/day of prednisone and daily injections of insulin.

The rapid improvement of the eruption after discontinuing metformin and glibenclamide suggested the possibility of the patient's hypersensitivity to these drugs. Other causes for leucocytoclastic vasculitis were ruled out as the laboratory results—antinuclear factor, latex, Rose-Waaler, C3, hepatitis B surface antigen, protein electrophoresis, and cryoglobulin—were negative or within normal limits.

The patient was admitted to the department of medicine two weeks after discontinuing prednisone. Metformin was reintroduced, and two days later an identical eruption was observed. This eruption disappeared progressively after metformin was stopped.

Comment

Vasculitis is one of the most common and severe forms of drug eruption.² The similarity between the experimental Arthus phenomenon and the

histological findings, in which fibrinoid and polymorphonuclear infiltrates are predominant features, suggests that immune complexes play a part in the pathogenesis of leucocytoclastic vasculitis.² The failure to find immunoglobulin in the lesion may have been due to its rapid clearance—that is, within eight to 18 hours—as in the Arthus phenomenon.

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Chylopericardium, chylothorax, and hypobetalipoproteinaemia

We describe a patient with chylous effusions in the pericardial and pleural spaces who also had familial hypobetalipoproteinaemia. A family study was performed.

Case report

A 21 year old woman had developed a symptomatic left chylothorax at the age of 9 (1973). A chest x ray film after aspiration showed that the heart was enlarged and pear shaped and an electrocardiogram showed low voltage complexes. Further cardiac investigations were recommended but not performed. After reaccumulation of the pleural effusion decortication of the left lung was performed. Preoperative lymphangiography and operative blue dye injections failed to disclose the site of leakage. There were no comments about the heart.

Over the next four years the patient was asymptomatic but chest radiographs showed further, progressive cardiac enlargement. She was admitted for investigation. Pericardial aspiration produced 270 ml chyle. After aspiration the heart size was normal. Serum lipid analysis was not performed.

Over the next three years the pericardial effusion reaccumulated. During three weeks in 1980 she developed anorexia, weight loss, lethargy, dyspnoea, and ankle swelling. On admission she was thin and pale and had the physical signs of a pericardial effusion. This was confirmed by echocardiography. Examination showed nothing else of note. Her haemoglobin concentration was 107 g/l with iron deficient indices and frequent acanthocytes in the blood film. Serum lipoprotein analysis (see table) showed hypobetalipoproteinaemia. Results of the chromium chloride test for protein losing enteropathy, faecal fat estimation, and findings on bipedal lymphangiography were normal.

Plasma low density lipoprotein cholesterol concentrations of members of reported family

Relationship to proband	Low density lipoprotein cholesterol concentration (mmol/l)	Comment
Proband:		
Preoperative	1.38	Hypobetalipoproteinaemia
Postoperative	2.00	Hypobetalipoproteinaemia
Sister 1	1.49	Hypobetalipoproteinaemia
Sister 2	0.96	Hypobetalipoproteinaemia
Mother	1.62	Hypobetalipoproteinaemia
Father	1.48	Hypobetalipoproteinaemia
Paternal aunt	2.06	Hypobetalipoproteinaemia
Paternal grandmother	2.78	Normal
Paternal grandfather	—	Dead
Maternal uncle	3.65	Normal
Maternal aunt	2.14	Borderline
Maternal grandmother	3.87	Normal
Maternal grandfather	3.11	Normal

Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38.6 mg/100 ml.

Laparotomy and exploration of the pericardium through an abdominal approach disclosed an area of lymphangiectasia 1.5 cm diameter in the small bowel mesentery. The pericardium was opened atraumatically and found to contain 1 litre of heavily bloodstained chyle (haemoglobin concentration 47 g/l). The pericardium was only slightly thickened and the heart normal. A pericardial window was formed.