tobacco industry has privately said, "the social acceptability issue will be the central battleground on which our case in the long run will be lost or won"[4] and therefore, of all the six policy objectives for smoking control proposed by the International Union Against Cancer,[5] an advertising ban is the measure the industry most strenuously resists. For health policy experts to accept advertising of low tar cigarettes is to permit the social legitimation of cigarette smoking to continue and give a totally unwarranted recommendation of the benefits of low yield cigarettes to adult smokers and to children taking up the habit. In particular, it has been suggested that low yield cigarettes increase the propensity of girls to start smoking,[6] a trend which has been noted in many countries.

Price policy and product modification are more effective than advertising for promoting the switch to lower tar and have less potential side effects. It may be that the government declines to implement the effective measures. It still remains the responsibility of medical opinion to inform the public of the scientific evidence and to refuse to support the advertising of low yield cigarettes, which could convey unfounded reassurances and blunt the powerful campaign mounted by the BMA for a total ban on cigarette advertising.

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Tobacco tarred gold?

SIR,—Minerva wonders (24 November, p 1459) whether or not research funding should be accepted from the ill named Health Promotion Research Trust and compares it to an American body, the Council for Tobacco Research. There are, however, important differences between the two organisations. The American council was established specifically to research into smoking whereas smoking is specifically excluded as a major research topic by the Health Promotion Research Trust. This exclusion, imposed by the tobacco industry that funds the trust, has been likened by one commentator to the Mafia funding research into the promotion of law and order but ruling out the topic of organised crime.[1]

The most important difference, however, is that the trust has an important role for the tobacco industry in its seeking to avoid further restriction of tobacco advertising and promotion. The tobacco industry established the trust in 1982 with funding of £11m—a price it was more than willing to pay to avoid such restriction. Indeed, the establishment of the trust was announced by the Secretary of State as part of a voluntary agreement with the industry. A secondary function of the trust has been to stimulate research into topics unconnected with smoking in health education and health promotion. Such generously funded research is designed to shift attention away from smoking, which, as we all know, is our largest preventable cause of death and disease. This attempt at buying off government and health professionals is to be achieved by providing a sum which is tiny in comparison with cigarette advertising budgets.

The medical profession has, however, rejected this chicanery. In July this year, at the Manchester annual representative meeting, the BMA overwhelmingly carried a motion recommending that no doctor or health authority should associate with the trust. The chairman of the BMA's board of science and education clearly stated that it was unethical for doctors to accept what he described as tobacco tarred gold. The director general of the Health Education Council has called it "blood money," and the trust has been overwhelmingly boycotted by established researchers in health promotion.

The BMA's recently launched campaign on smoking has been eagerly awaited and warmly welcomed. The battle is now joined to force the government to curb the activities of the "merchants of death." How regrettable it would be if, within sight of victory, the campaigners were stabbed in the back by greedy researchers whose concerns are limited to their departmental budgets.

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1 Coleman MP. Cigarette advertising. *Lancet* 1982;ii: 1106.

"Tobacco teabags"

SIR,—I should like to express my alarm at the recent introduction on to the English market of an American product called Skoal Bandits. These are individual portion packed pouches of mint flavoured smokeless tobacco. These tobacco teabags come with the recommendation that they be placed between the upper lip and gum, and left there for increasing lengths of time as the habit is acquired.

My cause for concern takes two forms. Firstly, this product is being advertised on television locally. It carries no health warning, statutory or otherwise, as other more conventional forms of tobacco do. My second and related point concerns the increased incidence of squamous cell carcinoma of the cheek associated with placing tobacco quids in the cheek.[1] Many other reports confirm this association, usually in relation to the betel quid. However, quid constituents (betel nut, betel leaves, and slaked lime) alone have not been shown to produce carcinoma. Only when tobacco is added is carcinoma the end result.[2] A study carried out by Cohen *et al* showed that histological changes, identical to those seen in early invasive lesions in betel quid users, were induced when tobacco was placed in cheek pouches of monkeys.[3] This is the position that is being recommended for Skoal Bandits.

At present in the United Kingdom oral carcinoma of the cheek is almost exclusively restricted to those Indian immigrants who still use betel quids or tobacco alone. It is an alarming prospect that widespread adoption of this or similar products may conceivably result in a much higher incidence of this particular type of cancer, a situation that has been predicted in the US,[4] where this habit is becoming increasingly popular.

I feel strongly that the medical and dental professions should take on the responsibility for alerting the general public, who may be led to believe that this product represents a "safe" alternative to more conventional tobacco products. A statutory health warning would go some way towards answering this problem, but only by widespread informed advice on this subject can we prevent smokers jumping "out of the frying pan into the fire."

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Serum cortisol concentrations during low dose dexamethasone suppression test to screen for Cushing's syndrome

SIR,—We read the paper by Dr L Kennedy and others (3 November, p 1188) with interest and an increasing sense of familiarity. Its content mirrors almost exactly the work reported by us in your journal in 1972 on plasma and urinary 11-hydroxycorticosteroids in the differential diagnosis of Cushing's syndrome.[1] The conclusions reached are likewise very similar, although, unlike the Irish authors, we found three patients, from a series of 19 with proved hyperplasia, who suppressed normally on low dose dexamethasone.

We believe that some reference should have been made to this work, which used appropriate non-Cushingoid controls, although admittedly it antedated the widespread use of radioimmune assays.

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1 Mattingly D, Tyler C. Plasma and urinary 11-hydroxycorticosteroids in differential diagnosis of Cushing's syndrome. *Br Med J* 1972;iii:17-21.

**Dr Kennedy and his colleagues reply below.—ED, *BMJ*.

SIR,—We acknowledge the points made by Professor Mattingly and Dr Tyler. The omission of any reference to their 1972 paper was an unintentional oversight on our part. We agree that our study design was similar to that in their paper in that both studies adopted the almost universally agreed protocol for the dexamethasone suppression test. There are, however, three essential differences between our studies. Firstly, as Professor Mattingly and Dr Tyler point out, we used the more specific radioimmunoassay for serum cortisol. Secondly, our comparison was with 24 hour urinary free cortisol, also measured by radioimmunoassay, which is accepted to be a more discriminating test than fluorometric measurement of 11-hydroxycorticosteroids. Finally, although Professor Mattingly and Dr Tyler included appropriate non-Cushingoid controls, they did not study a group of subjects with "possible" Cushing's syndrome—that is, people in whom there is a genuine suspicion that the syndrome may be present. As recourse to the low dose dexamethasone test is even more likely in these subjects, evaluation of

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the test, using the newer assay methods, is especially crucial in this group.

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Plasma theophylline concentrations, six minute walking distances, and breathlessness in patients with chronic airflow obstruction

SIR,—While no one would argue that the indiscriminate use of any drug in any condition is unjustifiable, we have serious doubts about the value of Dr W V Evans's study of theophylline in chronic bronchitis (15 December, p 1649). We supplied theophylline and placebo to Dr Evans but were given no opportunity to discuss his findings with him before publication. We do, however, possess the raw data. Our criticisms are as follows.

Firstly, patients who had greater than 20% improvement in peak expiratory flow rate (PEFR) or forced expiratory volume in one second (FEV_1) with β_2 agonists were excluded from his study. Addis *et al*, using the Medical Research Council clinical criteria for chronic bronchitis, found a maximal response to salbutamol of 58% in PEFR, 28% in FEV_1, and 48% in forced vital capacity (FVC), the last in their opinion being the most sensitive index of response.[1] Furthermore, they found that the response in FVC to theophylline alone, at steady state, peak, and trough plasma concentrations between 10 and 20 mg/l, averaged 125% of the maximal response to salbutamol alone. The fact that 14 of Dr Evans's 20 patients also had accompanying emphysema adds to the evidence that his selection criteria excluded bronchitics who would be likely to benefit from bronchodilator therapy. Given the marginal room for improvement, if any, in his patients the numbers in his trial are inadequate.

Secondly, he measured ventilatory response and six minute walking distance only once at 12 hours after a single dose of theophylline. Single measurements at one time point could miss an effect. A preferable design would be serial measurements over time at adequate steady state drug concentrations performed in an incremental fashion.

Thirdly, he found a significant increase in six minute distances between baseline and "placebo walks" and no significant increase in "theophylline walks." Unfortunately, we have found appreciable serum concentrations of theophylline in some of his patients (unpublished in his paper) supposedly on placebo alone. One of these patients had a serum concentration of 14·2 mg/l.

Fourthly, the fact that eight subjects complained of gastrointestinal disturbance when given 600 mg theophylline is not surprising. We recommend an initial week at 400 mg before using a higher dose.

When one examines the means and standard deviations of theophylline concentration, PEFR, FEV_1, and FVC, there is clearly a trend to improvement with dose, although individual values did not reach significance compared to baseline. The correlation of mean PEFR, FEV_1, and FVC with theophylline concentration produces correlation coefficients of 0·998, 0·996, and 0·991 respectively. We obtained an independent analysis of Dr Evans's data from a Cambridge University statistician, who found that serum theophylline, FVC, PEFR, and FEV_1 had a significant response to dose. These results are at variance with those of Dr Evans.

Dr Evans states that the role of theophylline in chronic bronchitis is less controversial than before, implying that it is overused. Others have found that it does produce benefit as measured by lung function tests and performance.[2–5]

In our opinion Dr Evans's study adds nothing to this debate but through its faults in design and conduct obfuscates the issue.

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**Dr Evans replies below.—ED, *BMJ*.

SIR,—Napp Laboratories kindly provided materials for my study only after examining the protocol themselves. No criticism of design was made then or later. All the analysed data conformed to the accepted double blind randomised format. Results for the 800 mg increment (not analysed) were single blind additions to avoid harmful side effects in subjects unable to tolerate such acute doses.

In spite of their claims, the results of the best walk for each day (not both) and of spirometry, with manuscripts, were forwarded to the company after the studies on the first 11 subjects had been completed (1983) and in spring 1984 on completing the series. I still await their reply. I entered no agreement regarding the conduct of the study and was not prepared to leave these important data unpublished.

In answer to their comments, my study was started before the quoted paper by Addis *et al* was published. The results took account of two walks for each incremental dose. Placebo theophylline concentrations are presented for all to see in the graph. In all but two subjects theophylline concentrations were not detected or were near the limits of detection (1 mg/l) and consistent with dietary sources. One individual recorded 4·5 mg/l (subtherapeutic in asthmatics) and another 14 mg/l (the patient quoted by Dr Miller and colleagues). He achieved concentrations up to 43 mg/l after 800 mg theophylline, raising the possibility that he had extremely slow clearance rates or was taking alternative medication.

Statistical methods and analysis were kindly provided by professional Cambridge statisticians, who also advised on interpretation. Individual spirometric function varied inconsistently with increasing theophylline dosage. By adopting the analysis of variance test, the blood drug value was found to explain 0·9% variation in FVC, 1·5% in FEV_1, and 0·4% variation in PEFR. Napp's team, using a different approach, do not mention the extent of spirometric improvement in their analysis, but should be able to do so.

The object of my paper was to determine whether theophylline influenced the disabling symptoms of effort intolerance in patients with poorly reversible airflow obstruction. No one disputes that small improvement in lung function is sometimes obtained with the drug, or that theophylline has an important role in chronic asthma. It was imperative therefore to exclude the latter from the study.

After more than 200 corridor walks incremental doses of theophylline failed to influence walking distances or associated breathlessness. Dr Miller and colleagues quote four references in support of theophylline, of which only one measured effort tolerance. This paper[1] was discussed in my manuscript. They failed to quote the later paper on this subject, whose results support my own.[2] Their reference 5 is irrelevant to this discussion and does not deal with theophylline.

I believe that long term theophylline in patients with poorly reversible chronic bronchitis should be reserved until individual placebo controlled studies of effort tolerance have shown definite benefit.

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1 Leitch AG, Morgan A, Ellis DA, Bell G, Haslett C, McHardy GJR. Effect of oral salbutamol and slow release aminophylline on exercise tolerance in chronic bronchitis. *Thorax* 1981;**36**:787-9.
2 Eaton ML, Macdonald FM, Church TR, Niewoehner DE. Effects of theophylline on breathlessness and exercise tolerance in patients with chronic airflow obstruction. *Chest* 1982;**82**:538-42.

SIR,—We agree with the limited conclusions of Dr W V Evans (15 December, p 1649), but it is unfortunate, given the considerable interest in methylxanthines,[1–4] that the study did not examine respiratory muscle strength or formally assess exercise ability. In an acute study we found no increase in maximal static mouth pressure development, unchanged maximal ventilation and oxygen consumption on exercise, and increased six minute walking distance and ventilatory sensitivity to inhaled CO_2.[5] In a subsequent study of chronic treatment walking distance was no longer increased and CO_2 responsiveness was unchanged. Maximal transdiaphragmatic pressure was not increased by active therapy in this study. We therefore believe that central actions of aminophylline may explain the acute benefit reported in some studies. We find no evidence for improved diaphragmatic performance with aminophylline.

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