Clinical and laboratory data on the two groups of patients with rheumatoid arthritis and Sjögren's syndrome. Values and means and ranges are given in parentheses

	Placebo	Levamisole
No of patients	8	10
No of men	1	2
Duration of rheumatoid arthritis (years)	10·9 (3-35)	21·2 (4-55)
Duration of Sjögren's syndrome (years)	2·6 (0·5-9)	3·8 (1-10)
No with history of drug allergy	3 (2 to gold, 1 to penicillamine	3 (1 to salicylates, 1 to gold, 1 to penicillamine)
Articular index	26·6 (11-54)	23·1 (11-65)
Duration of morning stiffness (min)	94·5 (15-300)	130 (10-420)
Digital joint circumference (mm)		
Right	287·1 (274-302)	289·5 (251-310)
Left	284·2 (266-306)	282·0 (244-329)
Grip strength (mm Hg)		
Right	96·7 (22-160)	108·3 (39-174)
Left	79·0 (36-160)	94·4 (37-170)
Pain level	2·3 (2-3)	2·3 (2-3)
Haemoglobin (g dl)	13·02 (11·4-16·2)	12·3 (10·2-14·0)
No positive for antinuclear factor	3	3
^{99m}Tc joint uptake (%)	3·13 (2·89-4·28)	3·66 (2·58-5·17)

withdrawn from patients who have responded well after six to nine months their condition will deteriorate. Some weeks after stopping treatment synovitis reappears with increasing pain and tenderness and loss of function ability (Dr El-Ghobarey; unpublished observations). Thus it seems more likely that levamisole is suppressing disease activity rather than removing the basic cause.

Levamisole is undoubtedly a toxic drug. Side effects seem to be more common in patients with connective tissue disease than in those without.[1] Our results are so striking that we felt it important to report them immediately. We have not been able to show laboratory evidence that the skin rashes were indeed immunologically mediated, although this does seem to be the most likely pathogenesis. The patients who developed an influenza like illness with muscle pains and weakness are more difficult to explain. They had not experienced a similar illness before and the fact that the syndrome recurred on re-exposure indicates that this syndrome was probably related to levamisole. These patients did not develop a rash or proteinuria nor was their muscle weakness clinically like myasthenia. Levamisole may exert an effect on the cyclic adenosine monophosphate membrane system[1] and this may be relevant. Muscle enzyme concentrations (serum alanine transaminase, aspartate transaminase, creatine kinase) did not rise in these patients.

We have had the clinical impression for some time that hypersensitivity to levamisole, as with other drugs,[5] might be more common in patients with rheumatoid arthritis complicated by Sjögren's syndrome than in those without. Our results amply confirm that clinical impression. Although the numbers developing side effects were small, the proportion of the total treated was too large to be ignored. The results suggest that levamisole should be prescribed with considerable caution, if at all, for patients with rheumatoid arthritis complicated by Sjögren's syndrome.

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CONDENSED REPORT

Effect of cigar smoking on carboxyhaemoglobin and plasma nicotine concentrations in primary pipe and cigar smokers and ex-cigarette smokers

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Summary

Five ex-cigarette smokers and five primary pipe and cigar smokers each smoked a large cigar. Carboxyhaemoglobin (COHb) and plasma nicotine levels were measured. In the ex-cigarette smokers mean COHb rose from 2·9% to 9·6% and plasma nicotine from 79·0 nmol/l to 281 nmol/l (12·8-45·6 ng/ml). This response was similar to that of cigarette smokers smoking cigarettes, which indicated that the subjects had inhaled and absorbed significant amounts of nicotine. In the primary pipe and cigar smokers the mean COHb rose from 0·8% to 1·0% and the plasma nicotine from 21 nmol/l to 32 nmol/l (3·4-5·2 ng/ml), indicating neither significant inhalation nor significant nicotine absorption.

Since ex-cigarette smokers do not seem to lose their habit of inhaling when they change to cigars, measures aimed at persuading smokers to switch to cigars will have little effect on their health. Pipe and cigar smokers who have never smoked cigarettes do not inhale, which probably accounts for their reduced incidence of coronary heart disease and lung cancer. But they also appear not to absorb nicotine, which suggests that nicotine is absorbed largely from the lung and that the buccal mucosa is unimportant. It also raises the interesting question of why primary pipe and cigar smokers do smoke.

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Introduction

Primary pipe and cigar smokers have only slightly greater mortality rates than non-smokers.[1-3] It is believed that they

smoke to obtain nicotine, but, as they do not inhale, the alkalinity of the pipe and cigar smoke allows nicotine to be absorbed via the buccal mucosa. Their lower mortality is thought to be due to the fact that they do not inhale. Changing from cigarettes to cigars would be beneficial only if the former cigarette smokers smoked cigars in the same way as primary pipe and cigar smokers—that is, without inhaling. There is, however, evidence to suggest that they continue to inhale.[1-6]

We carried out the present study to assess the degree of inhalation in true primary pipe and cigar smokers and compared it with that of ex-cigarette smokers when they each smoked one large cigar. We used blood carboxyhaemoglobin (COHb) concentrations as an indication of inhalation and plasma nicotine levels to estimate the amount of nicotine absorption.

Subjects and methods

Ten men, who were members of the hospital staff (nine physicians and one cardiological technician), took part in the study. Five were ex-cigarette smokers who had stopped smoking cigarettes three to 17 years earlier; all had smoked an occasional cigar since and two were now regular pipe smokers. Five were primary pipe and cigar smokers who had never smoked cigarettes. Full details of their smoking histories are shown in table I.

The subjects were studied at the end of a normal working day. They were asked to refrain from smoking for at least six hours before the study. Light refreshments were provided before and throughout the period of smoking to create a more typical situation for the smoking of large cigars. The cigars used were petit coronas, made of Havana tobacco. They were 12·4 cm long and weighed on average 6·20 g. Pretrial investigations indicated that the average smoking time for this cigar was one hour. Venous blood samples were obtained immediately before smoking and at 20, 40, and 60 minutes, after which the cigar was extinguished without crushing the butt. Further venous blood samples were obtained one hour after cigar smoking. Thereafter the subjects smoked freely and a final venous blood sample (for COHb determination only) was taken the next morning.[7] Plasma nicotine levels were analysed by gas-liquid chromatography[8] by Hazelton Laboratories, Europe. The length of unburnt tobacco in the cigar butt was measured.

The results were analysed statistically using Wilcoxon's rank sum test.[9]

Results

The primary pipe and cigar smokers had a shorter interval since last smoking (mean 14 hours) compared with a mean of 4·7 days in the ex-cigarette smokers, but their pre-smoking COHb levels were lower (mean 0·8%) as well as their plasma nicotine levels (mean 21 nmol/l (3·4 ng/ml)), although these differences were not significant.

In the primary pipe and cigar smokers the mean COHb levels increased from a presmoking value of 0·8% to a maximum of 1·0% during smoking and fell to 0·6% by the next morning. The plasma nicotine levels showed a similar small increase from a presmoking mean of 21 nmol/l (3·4 ng ml) to a maximum of 32 nmol/l (5·2 ng/ml), falling to 28 nmol/l (4·5 ng/ml) after stopping smoking for one hour (table II).

In the ex-cigarette smokers the mean COHb levels rose from 2·9% to a maximum of 9·6% after smoking for one hour and fell to 3·5% by the next morning. The mean plasma nicotine levels rose from 79 nmol/l (12·8 ng/ml) to a maximum of 281 nmol/l (45·6 ng/ml) at 40 minutes, falling to 153 nmol/l (24·8 ng/ml) after stopping smoking for one hour. The difference between the COHb and plasma nicotine levels in the primary pipe and cigar smokers and the ex-cigarette smokers were significant at all times during smoking (table II).

The mean butt lengths were shorter in the primary pipe and cigar

TABLE I—*Smoking histories of subjects studied*

Subject No	Age (years)	Past smoking history: Type	Past smoking history: Amount	Past smoking history: Age started (years)	Present smoking history: Type	Present smoking history: Amount	Years since last cigarette smoked	Time since last smoked
Ex-cigarette smokers								
1	30	Cigarettes	10–15 day	15	Small cigar	2 day	3	2 days
2	30	Cigarettes	20–30 day	16	Medium cigar	2 month	6	2 weeks
3	46	Cigarettes	15 day	21	Large cigar	1 week	18	1 week
4	33	Cigarettes Pipe tobacco	20 day 85 g week	17 17	Large cigar Pipe	3 week 85 g week	14	6 hours
5	31	Cigarettes Pipe tobacco	10–15 day 28 g week	22 26	Pipe	28 g week	5	7 hours
Primary pipe and cigar smokers								
6	50	Large cigars Pipe tobacco	1 day 57 g week	41 18	Large cigars Pipe	1 day 71 g week	Never	20 hours
7	30	Small cigars Pipe tobacco	4 day 57 g week	24 28	Medium cigars Pipe	1 day 114 g week	Never	8 hours
8	27	Small cigars Pipe tobacco	2 day 43 g week	21 21	Small cigars Pipe	5 week 43 g week	Never	9 hours
9	29	Pipe tobacco	28 g week	17	Medium cigars Pipe	1 week 28 g week	Never	15 hours
10	33	Large cigars Pipe tobacco	1 month 28 g week	20 20	Large cigars Pipe	2 month 28 g week	Never	19 hours

TABLE II—*Mean carboxyhaemoglobin and plasma nicotine concentrations in five ex-cigarette smokers and five primary pipe and cigar smokers before, during, and after smoking a large cigar*

		Before	20 min	40 min	60 min	2 h	Next morning
Plasma nicotine (nmol/l)							
Ex-cigarette smokers	Mean	79·0	189·3	281·3	223·6	152·6	
	Range	18·5–207·4	35·2–411·7	64·2–728·3	82·7–327·1	42·0–224·7	
Primary pipe and cigar smokers	Mean	20·5	24·8	26·4	31·6	27·6	
	Range	15·4–27·2	15·4–39·5	20·4–42·0	28·4–38·3	21·0–37·0	
P value		NS	<0·05	<0·01	<0·01	<0·01	
COHb (%)							
Ex-cigarette smokers	Mean	2·9	6·6	8·4	9·6	8·1	3·5
	Range	0·8–6·7	1·4–12·1	2·3–13·4	2·5–13·8	2·2–11·7	1·5–5·8
Primary pipe and cigar smokers	Mean	0·8	1·0	1·0	0·9	1·0	0·6
	Range	0·3–1·5	0·4–1·9	0·3–2·2	0·3–1·5	0·4–2·0	0·3–1·2
P value		NS	<0·05	<0·01	<0·01	<0·01	<0·01

Conversion: SI to traditional units—Nicotine: 1 nmol/l ≈ 0·162 ng/ml.

group (mean 3·4 cm) than in the ex-cigarette group (mean 3·7 cm). The detailed results are shown in table A* and the group values for COHb and plasma nicotine in fig *a*.

Discussion

The rise in COHb concentrations of ex-cigarette smokers while they smoked one petit corona showed that they both inhaled significantly and absorbed nicotine. The increases were much higher than those found after smoking one medium-tar nicotine cigarette.[10 11]

Although cigarette smokers have been found to continue to inhale when smoking small cigars,[4 5] we were surprised that our subjects did so when smoking large cigars. Earlier studies[4 5] included people who had changed from cigarettes to cigars fairly recently, whereas our subjects had stopped smoking on average nine years earlier. Despite Freedman's report of an ex-smoker who smoked large cigars and continued to inhale,[6] it has generally been thought that the smoke of large cigars is too irritating to inhale. Our findings and those of others[4-6] seem to suggest that cigarette smokers who are used to inhaling will continue to do so when they change to cigars, regardless of their size. This suggests that there would be no health benefit in trying to persuade cigarette smokers to change to cigars of any size.

The primary pipe and cigar smokers had low COHb levels throughout the study, confirming that they did not inhale. The reduced mortality in primary pipe and cigar smokers probably relates to this fact. Not only did the primary pipe and cigar smokers not inhale, they also absorbed very little nicotine. The small rise in plasma nicotine in this group was similar to that found in passive smoking[12] and would be expected in the environment of this study. The failure of the primary pipe and cigar smokers to absorb nicotine from the large cigar suggests that extrapulmonary routes of absorption of nicotine from smoke are unimportant.

It had been suggested that buccal absorption of nicotine from smoke is significant.[1] Armitage and Turner[13] found that nicotine in an alkaline aqueous solution could be absorbed via the buccal mucosa of a cat, and Russell *et al*[14] found that a nicotine-containing chewing gum that had been buffered to a pH of 8·5 allowed buccal absorption of nicotine in man. It has been assumed that these findings could be extrapolated to nicotine in smoke, but our findings suggest that, for the cigars used in this study, this extrapolation is not justified. Although there is no detailed smoke chemistry analysis available on the cigar we used, the composition of the cigar is not unusual and we see no reason why the smoke chemistry should be different from that of other cigars. Buccal absorption of nicotine from smoke would require that the nicotine from the smoke passing transiently through the mouth be absorbed in adequate quantity in saliva, and that the relatively alkaline cigar smoke (pH about 8·3-9) alkalinises the saliva so that absorption could take place. The normal pH of saliva is 5·8-7·1.[15] The buffering capacity is probably such that a small quantity of alkali in cigar smoke would not alkalinise saliva.[16] Thus even if the quantity of nicotine dissolved in saliva were adequate, the pH most appropriate for absorption would probably not be attained. As the primary pipe and cigar smokers do not inhale and the conditions for significant nicotine absorption from the buccal mucosa are almost certainly not realised during smoking it is perhaps not surprising that they do not absorb significant amounts of nicotine, although this finding is unexpected.

Our group of primary pipe and cigar smokers were as "addicted" to their pipes and cigars as inhaling cigarette smokers are addicted to their cigarettes. In our study they tended to smoke more of the cigars than did the ex-cigarette smokers. The interval since their last smoke was shorter. Their "addiction" in the absence of evidence of nicotine absorption is a remarkable finding and clearly requires further investigation. The low pre-smoking nicotine levels in this group strengthens the view that this is a significant finding.

We conclude that cigarette smokers who change to cigar smoking do not lose their habit of inhaling even after many years. The health benefit of such a change must be uncertain. The absence of inhalation by primary pipe and cigar smokers probably accounts for their smaller risk of heart and lung disease, but the accompanying absence of nicotine absorption makes their motive for smoking an enigma.

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Copies of the unpublished table and figure are available from Dr M W McNicol, Cardiothoracic Department, Central Middlesex Hospital, Acton Lane, London NW10 7NS.

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*Copies of table A and figure *a* are available from the authors.

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