Nitric oxide (NO) is one of the principal components of the gas phase of cigarette smoke. Fresh cigarette smoke does not contain nitrogen dioxide (NO₂) (1). This is because, at 600°C, (the minimum temperature in a cigarette burning tip during smoking), the breakdown of nitrogen dioxide into nitric oxide and oxygen is complete (2). Workers who have detected nitrogen dioxide in the smoke have invariably allowed the smoke to age before analysis (3). The concentration of nitric oxide is up to about 1000 parts per million (ppm) varying greatly with the type of tobacco from which the cigarettes made.

Nitrogen dioxide is well known to cause emphysema in experimental animals following prolonged low level exposure (4). In general a minimum of about 5 ppm NO₂ is required to produce this specific biological change though ultrastructural and biochemical changes have been produced by lower concentrations. Whilst nitrogen dioxide in higher concentrations causes a toxic pneumonitis in man (silo fillers lung) (5), the long term effects of lower concentrations are less clear cut. As far as we are aware, low concentrations of nitric oxide (NO) have not been associated with emphysema in experimental animals, but some of the earlier work is hampered by workers not ensuring that the exposure chamber is free of contaminating nitrogen dioxide (NO₂). If nitric oxide (NO) in the smoke is to cause emphysema in smokers, conversion to nitrogen dioxide (NO₂) would be required. Oxidation of nitric oxide in air at concentrations of 1% and above is instantaneous but slows markedly as the concentration of nitric oxide falls:

\[-d(\text{NO})/dt = 2k(\text{NO})^2(\text{O}_2)\] where \(k = 1.2 \times 10^9 e^{-530/T}\) (6)

(where \(T\) is temperature in degrees k). Thus at 1,000 ppm the half life of NO in air is three minutes and at 20 ppm is 2.6 hours. Since during normal smoking the smoke is held in the mouth and lungs for only a few seconds, and is diluted several fold by fresh air during the act of inhaling, little NO₂ should be generated. However the rate of oxidation of NO in tobacco smoke or within the respiratory tract is unknown.

We have used a chemiluminescent analyser to study the rate of oxidation of NO in the gas phase and the whole smoke of a standard UK middle tar cigarette. The analyser (Chemilab Ltd) generates ozone and any nitric oxide in the sample is oxidised to NO₂ in an excited form which, on returning to the ground state emits light which is then quantified by a photomultiplier. The smoke was generated by a standard single port restricted smoking machine (Heinrich Borgwaldt) taking a 35 ml bell shaped puff of 2 seconds duration. The third puff from the cigarette (empirically found to have the most reproducible concentration) was allowed to age from varying periods of 0 to 10 minutes. Since the analyser consumed the puff during analysis only one observation per puff was made. Two observations were made for each one minute interval between 0 and 10 for both gas phase and whole smoke and the order randomised. The disappearance of nitric oxide in the whole smoke closely conformed to the predicted kinetics for air after adjusting for the oxygen concentration (14.4%) in smoke.

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which was measured in a separate experiment using a mass spectrometer (Centronics 200 mgA). In the gas phase, the rate of disappearance was rather faster and appeared to follow 1st order kinetics with a half life of 257 seconds. The only species present in the cigarette smoke which will oxidise nitric oxide faster than oxygen and by a 1st order mechanism are oxygen centred free radicals. Our observations suggest that in isolated gas phase these species are continuously regenerated but in whole smoke the particulate matter inactivates them so that oxidation then proceeds by the usual mechanisms for air.

To study the fate of nitric oxide when inhaled in low concentrations a single breath technique was devised. Three volunteers inhaled from functional residual capacity varying volumes of a helium/air/nitric oxide mixture and after a 10 second breathhold exhaled to FRC. No uptake of NO occurred until volumes in excess of predicted dead space had been inhaled: with larger volumes inhaled NO was almost completely retained. We conclude that oxidation of nitric oxide in the airways proceeds no faster than in air and that uptake only takes place from the alveoli. To study this mechanism further 15 volunteers inhaled a single vital capacity (VC) breath of helium/air/NO/carbon monoxide (CO) mixture from residual volume (RV) and after a 7.5 second breathhold exhaled to RV. The standard physiological index of CO gas transfer (DLCO) was derived as was an index of NO transfer. Values for DLCO and DL NO were closely correlated. Extending the study to five subjects at rest and at three levels of exercise significant increases in both DLCO and DL NO occurred, with increasing exercise. This suggests that inhaled NO, like CO, is rapidly transferred from alveolus to blood rather than reacting with lung components like NO2.

This view is supported by a survey of NO yields in commercial cigarettes. Fourteen popular UK, 14 popular US and eight popular French brands were analysed for nitric oxide by a standard method (7). The nitric oxide yield for UK cigarettes was one third of those of US or French cigarettes which were similar. We then examined the male age specific mortality from chronic bronchitis (ICD A93) in 20 developed countries (8). Because of the tendency for some countries (eg US) to classify bronchitis mortality under "other lung diseases" this category was added to A93 and the total rate per 100,000 men for the cohort aged 55-64 in 1975 taken. Tobacco consumption for this cohort was estimated by national cigarette consumption for the years when they entered adult life (9, 10). In general bronchitis mortality and tobacco consumption were related but mortality was paradoxically higher in countries where UK type cigarettes of low nitric oxide yield are smoked than where US or French type of high nitric oxide yield are preferred. Our findings are against a role for nitric oxide in cigarette related obstructive lung disease. It has been suggested that reduction of nitrate in tobacco may produce a "safer" cigarette with low nitric oxide and volatile nitrosamine yield (11). Because of our findings and the uncertain status of nitrosamines as carcinogens in smokers we do not believe such a step to be beneficial, since a reduction of nitrate may lead to an increase in polyaromatic hydrocarbons (12) and a decrease in smoke ammonia (13), and hence pH, it could be harmful.

REFERENCES
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