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The concept of producing a non-combustible cigarette has recently been raised. One interpretation of a non-combustible cigarette is a device designed to deliver nicotine by the inhalation route. As the act of cigarette smoking is extremely complex in terms of physiology, pharmacology and psychology, simply inhaling nicotine is unlikely to be a substitute for cigarette smoking, but it does provide a starting point for the non-combustible cigarette project.

#### Devices for delivery of nicotine

There are two possible methods of delivering nicotine aerosols: nebulisers using aqueous solutions and metered dose aerosols using freon propellants.

##### (a) Nebulisers using aqueous solutions

Nicotine delivered as an aqueous aerosol from a conventional nebuliser is the cheapest and most versatile means of delivery. Various types of nebulisers are currently available, ranging from compressed air driven devices such as the Wright nebuliser to ultrasonic devices such as the De Vilbiss. Different types of nebulisers give different aerosol characteristics - i.e. particle size and amounts delivered. Similarly for a given nebuliser the concentrations of nicotine aerosols could be widely varied by altering either the concentration of the nicotine solution or the output of the nebuliser. Although the conventional nebuliser approach could never materialise into a "non-combustible cigarette", it would provide dose-ranging information.

##### (b) Metered dose aerosols using freon propellants

Metered dose aerosols have revolutionised the treatment of respiratory disorders such as asthma and bronchitis. The devices are compact (smaller than a packet of cigarettes) and extremely simple to operate. The drug and a propellant (usually freon) is contained in a pressurised canister and is released by operating a valve which is designed to give a specific volume of aerosol for a set time. Most metered dose aerosols require the user to actuate the valve by hand and co-ordinate the delivery of the aerosol with his inhalation. However, the pharmaceutical industry, particularly Riker's, have developed "breathe actuated devices". These devices are placed to the mouth and offer a resistance to airflow. When the subject attempts to inhale through the device, a pressure differential is created and this can actuate a spring mechanism which in turn opens the valve of the device. A modification of this type of device may produce a suitable delivery vehicle for the non-combustible cigarette. The biggest problem with a metered dose aerosol approach is the production of aerosol cans containing nicotine and propellants. Clearly, we do not have the necessary experience or equipment at GR&DC to manufacture and perform stability and quality control tests on such an aerosol. Commercial pharmaceutical organisations such as Riker's manufacture aerosol cans and valves for the

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pharmaceutical industry and for a suitable fee would probably produce nicotine aerosols for us. If we were to take this approach we would have to have information on nicotine doses, etc., before aerosol cans were prepared - i.e. we would need information from an aqueous aerosol study initially.

Guidelines for a nicotine aerosol study

The main objective of a study would be a comparison of the physical properties of the mode of nicotine delivery, i.e. cigarette vs. aerosol devices, the resulting physiological and subjective effects and the pharmacokinetics of nicotine delivered by the different methods.

(a) Physical properties

These would include parameters such as particle size, nicotine concentrations and pH of smoke vs. pH of aerosol.

(b) Physiological parameters

Many physiological parameters must be recorded during the study. These include ventilatory pattern, indices of lung function, ECG, blood pressure, an index of peripheral blood flow and possibly cardiac output.

(c) Subjective sensations

Some subjective sensations during and after the inhalation of nicotine aerosols should be compared with those produced by cigarette smoke. These could include sensations such as mouth and throat irritation, impact, light-headedness or dizziness and nausea.

(d) Pharmacokinetics

By controlling the output of the nebulisers and inhalation depths and durations it should be possible to match nicotine deliveries by nebuliser to those produced by cigarettes. However, an index of the amount and rate of uptake of nicotine would be required. Measurement of nicotine and its metabolite levels in plasma and urine should provide this information.

Ideally, the initial work on nicotine aerosols should be done within GR&DC. Unfortunately, studies outlined in this memo present certain ethical problems. Although the preparation and delivery of aqueous aerosols together with the physiological monitoring could be performed at GR&DC, is it ethical to allow subjects from GR&DC to inhale nicotine aerosols? Secondly, a pharmacokinetic study would involve taking blood samples from the subject, a procedure which is not allowed at GR&DC.

There are two possible solutions to these problems.

- (a) We perform the experiments at GR&DC with a medically qualified person in attendance.
- (b) We perform the experiments in a clinical environment in conjunction with an external group containing medically qualified personnel.

I would like some advice on how to tackle these ethical problems in order to make a start on this project.

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