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SYNOPSIS OF: "Nicotine And The Smoker"

A review paper by: Professor David M. Warburton

(to appear in 'Reviews On Environmental Health' early next year)

1. Background

This lengthy but informative review of the role of nicotine in the smoking habit is based essentially on Professor Warburton's comprehensive, 112-page, 1982 unpublished report entitled "Nicotine And The Smoking Habit", cited as reference 28 in the 3rd report of the ISC. The conditions under which nicotine exerts its actions are well described in the current paper. The review of the basic pharmacokinetics and pharmacodynamics of nicotine is commendable. It is erudite, and clearly written for experts in the field. What makes the paper unusual is the fact that it features the virtues of nicotine, and contrast its unique properties by a favourable comparison with other socially used substances. In other words, it highlights the benefits of smoking.

2. Essential Message

Its thesis is that nicotine has positive effects, and it explains that smoking releases hormones which reduce fatigue and acts on the central nervous system (basically the brain) to produce what it terms "more efficient processing of information". This increased efficiency produced by nicotine enables smokers to perform better in their work situations. In addition, nicotine can have a sedative action reducing anxiety and anger. At the same time, the pharmacokinetic properties of nicotine make smoking doses remarkably safe for normal healthy adults, and so there is a high benefit-risk ratio for nicotine versus other substances of use. It concludes that the unique pharmacological properties of nicotine make it an ideal substance of use, and advocates that the development of a medium nicotine cigarette with added flavour but with reduction of some smoke components could represent an important milestone on the way to a better cigarette.

3. Aim of this Synopsis

Below, we have attempted to extract points pertinent to the industry, without labouring esoteric technical detail. This is not

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because the technical detail is unimportant, it was most necessary to the review, but because it is largely inappropriate to the intention of this synopsis. Mostly, we have taken sentences verbatim from the review, to avoid distorting their content. Some have, however, been restructured slightly for ease of reading, without (intentionally) upsetting their tenor. Points need not necessarily appear in the same sequence as they were made in the review. Headings have been added for convenience.

4. Importance of Nicotine

Professor Warburton explains that in the current climate of political and medical opinion, it is not surprising that researchers are reluctant to state publicly that smoking can have any positive effects for the smoker, and yet common sense argues that it must. He advocates that the belief of smokers about the beneficial effects of smoking is substantiated by this review of the literature on nicotine and the smoking habit.

It is stated that nicotine is the most potent psychoactive agent in tobacco smoke. Although it cannot be concluded that flavour from the 'tar' of tobacco smoke plays no part in cigarette acceptability, nicotine is an essential ingredient of the cigarette for the smoker.

5. Nicotine Absorption

A crucial part of cigarette smoking is smoke manipulation by inhaling. The major site of nicotine absorption for the majority of smokers is the lungs. Some nicotine is absorbed from the nose but it is a small amount in comparison with inhalation. Gastric absorption only plays a small part in nicotine uptake from cigarette smoking in normal circumstances. Nicotine intake can be controlled by the amount of smoke inhaled as well as by cigarette consumption and by the mode of smoke generation. The mechanisms are not necessarily interdependent; but, as far as nicotine absorption is concerned, inhalation is the final control on intake.

6. Individual Nicotine Control

Inhalation enables the efficient transfer of nicotine from the tobacco to the smoker's bloodstream. Nicotine is absorbed very efficiently, enters the brain very quickly, and is metabolised (i.e., de-activated) quickly by the liver, giving a brief duration of action. Smokers are sensitive to their blood nicotine levels, and can control their intake of nicotine. Smokers control nicotine by varying their cigarette consumption, their strength of puffing, and their

brain?

no evidence for inhalation pattern change.

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inhalation. Smokers have quite precise personal control over nicotine intake. Nicotine intake is titrated to obtain, for example, more nicotine from lower yielding cigarettes and less nicotine from higher yielding brands.

The behaviour of a smoker is the outcome of a complex set of interactions. It is determined not only by the characteristics of the situation, but also by the personality of the individual. Thus, lighting a cigarette, and the pattern of smoking behaviour controlling nicotine intake, depends on what may be termed 'the individual situation interaction'. Depending on the situation, smokers will adjust their smoking behaviour in terms of the number of cigarettes smoked, smoke generation, and amount of smoke inhaled, to control the nicotine levels reaching their brain, and in this way their psychological state.

maybe not.

Measures of smoking behaviour during work performance and while subjects are under stress show that smokers vary their nicotine intake according to the situation. Studies suggest that people use substances which fulfil their own individual needs, and research argues persuasively that people titrate nicotine to obtain a specific dose to fit their needs. Some smokers smoke in anticipation of a future need. Evidence for control over the nicotine dose is important; it argues not only for nicotine being a necessary condition for smoking but also that smokers are trying to obtain a dose which will produce desired or needed effects.

7. Nicotine and Mental Functioning

Questionnaire surveys have shown that desires for stimulation and for sedation are major smoking motives. Smoking motive questionnaires indicate clearly that smokers believe that smoking helps them to think and to concentrate, and experimental studies have shown that smoking can indeed produce absolute enhancements in work performance, as well as preventing performance decrements. In addition, smoking enhances both cognitive precision and reaction time (i.e., there is no speed and accuracy trade-off), resulting in an overall improvement in mental processing efficiency. The evidence is that nicotine helps a person to ignore distracting information and so concentrate on relevant information. In 'brain wave' studies of electrocortical activity (conducted by Professor Warburton's own Department), it has been found that cigarettes (and nicotine tablets) increase the brain's alert pattern similar to that found when a person is concentrating. At the same time, concentration performance was improved. Thus, smokers claim that they smoke to help them think and concentrate, and nicotine's action on the brain produces the neural state for satisfying this need. Therefore data support the subjective experience of smokers that smoking helps them to concentrate. Nicotine is the most likely

this is Controversial. Maybe no better than non-smokers

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constituent of cigarettes for producing improvement in performance.

Smokers also believe that smoking is beneficial when they are anxious, and there is much evidence for the tranquillizing action of smoking. A large body of evidence indicates that smokers smoke in order to reduce anxiety, and smoke more and presumably take more nicotine when under stress. Certainly, anxiety-prone individuals smoke more intensely, and studies show that nicotine helps them cope better. Conversely, the smoker who is deprived of nicotine is less calm. The hypothesis is that nicotine is the tranquillizing ingredient of cigarette smoke.

Nicotine seems to be a unique substance because it combines both performance enhancement with anti-anxiety and anti-anger action. Individuals adjust their smoking behaviour to the amount of nicotine required for a particular brain state and so control their psychological state. The desired state will depend on the outcome of interaction between the individual and the situation. By adjusting the nicotine dose, the same individual may use a cigarette to provide a 'stimulant' effect on one occasion and a 'sedative' effect on another. Smokers have learned that to control their mood by smoking will enable them to function more efficiently on some tasks and will help them avoid the undesired consequences of other situations, and so anticipatory smoking (cf. Section 6 above) can be seen as a rational coping strategy on the basis of their past experience.

8. How Nicotine Possibly Works

In order to act on the brain, a substance must penetrate what is called the 'lipid blood-brain barrier'. Nicotine passes through this barrier extremely efficiently. Virtually all the nicotine that is delivered to the brain leaves the blood. As a result of this efficient uptake of nicotine, doses affecting the brain can be obtained with relatively low blood levels, which minimises the risk of toxicity to other organs. The brain does not metabolise nicotine (i.e. chemically change it), rather nicotine washes out quickly from the brain, which gives a short duration of action. Thus nicotine is a substance which is rapidly absorbed into the brain, widely distributed, and then quickly removed; the ideal specification, in fact, for a substance that is required for a short duration of action.

how do we know what an effective brain dose is?

Changes in neurochemical activity in the brain alter the way in which a person interacts with his or her environment, and so psychological performance reflects both the nature of any substance used and the biochemical state of the person. There is evidence that nicotine produces changes in the brain levels of neurotransmitters such as catecholamines, indoleamines, and acetylcholine. This is particularly true of the last, for the major effect of smoking doses is

reference?

increased cortical release of acetylcholine. However, the shifts in cortical activity are within normal limits, and are indistinguishable from that seen when a person is concentrating hard. Thus, smoking doses of nicotine precisely mimic acetylcholine, and produce the same neural changes that would occur after natural activation of some synapses (the nerve junctions). The reason for this exact mimicking of acetylcholine by nicotine at some synapses is the remarkable similarity between the structures of the two molecules.

does nicotine release ALL or replace ACh, or both

The benign action of nicotine in improving psychological performance could therefore be due to this molecular similarity between nicotine and acetylcholine, so that nicotine acts in a natural way on neurones (the nerve cells) and only produces changes in the brain which occur normally in states of alertness. Certainly, the most consistent effect with smoking doses of nicotine is stimulation of certain neurones (a subset of the cholinergic, called the 'nicotinic' pathways). As a consequence of nicotine's similarity to acetylcholine, tolerance to its action does not occur. (Tolerance is the term for 'pharmacological resistance', the phenomenon whereby ever-increasing doses of a substance have to be applied to induce the same effect as previously.) This lack of tolerance is not surprising because the brain's neurones cannot become tolerant to their own transmitters, otherwise the brain would cease to function. This lack of tolerance might explain why smokers do not increase their smoking over the years. Nicotine thus has low abuse potential, and smoking enables smokers to have exquisite personal control over their psychological functioning.

No! amphetamine releases NAdren (natural) but is not benign

Not so.

Yes they can.

9. Nicotine's Innocuity and Attractive Properties

When evaluating nicotine use and the smoking habit, it is interesting to compare nicotine with substances which produce 'similar' effects. Reference substances chosen for comparison (by Professor Warburton) are two stimulants (amphetamine and caffeine), two sedatives (alcohol and diazepam, i.e. Valium), and a euphoriant (marijuana, of which the active ingredient is called tetrahydrocannabinol, THC for short). (The review goes into considerable technical detail of the pharmacokinetic and pharmacodynamic properties of all these substances in order to put nicotine use into perspective, but only salient points relating primarily to nicotine will be featured here.)

This is only because of the dosing method i.e. inhalation for nicotine.

Firstly, nicotine reaches potential active sites in the brain very quickly in comparison with these reference substances. From the evidence available, smoking doses of nicotine only act directly on specific systems in the body (i.e. some of the acetylcholine systems, the so called 'nicotinic' pathways - see Section 8 above). This specificity of action decreases the likelihood that nicotine will produce unwanted 'side-effects'.

What about release of other neurotransmitters?

Also, absorption time is important for personal control of effect, and prevention of over-dosing: nicotine is metabolised (broken down) very efficiently by the liver, which limits nicotine's duration of action in the body. The metabolites (i.e., the by-products) appear to be virtually inactive, and so the pharmacological effects are determined almost completely by the action of nicotine alone. In contrast, diazepam and marijuana have active metabolites, which prolong their action.

An ideal substance of use would enable the person to fit the dose to his/her needs. Smokers have puff-by-puff control, with brain effects occurring within 10 seconds. A drinker of alcohol, on the other hand, must choose an appropriate dose for effects in an hour or so. Thus, in terms of personal control, the experienced smoker has precise control over nicotine's psychoactive effects, whereas most drinkers have very haphazard control. Clearly, nicotine fits the specification of a substance which people can use to exert fine control over their psychological states on an hour by hour basis (unlike marijuana, in particular, the effects of which linger for days with concomitant adverse consequences).

Abuse potential is an important consideration: An abuser is a person who is consuming a substance in sufficient quantities to produce damage to health. A comparison of the number of users and abusers is difficult because nicotine, caffeine, and alcohol are readily available, while amphetamine and diazepam are controlled, and marijuana is illegal. When amphetamines were freely available on prescription in Britain, about 20% of the users were abusing them. Alcohol and caffeine are socially acceptable substances in most Western cultures, and in these about 6% abuse alcohol and about 3% are caffeine abusers. It is estimated that about 6% of marijuana users are abusers. Abusers of diazepam are rare, current estimates are less than 1%. Strictly speaking, the number of abusers of nicotine is zero since few individuals take nicotine alone, and nicotine is not considered to contribute to smoking-associated diseases.

Where can nicotine alone ~~be~~ be obtained by the public?

Nicotine, as used by the smoker, is a low risk substance in terms of acute and chronic toxicity, nicotine in smoking doses having little known toxicity itself (the 1981 TAC Monograph on Nicotine by Drs. Cohen and Roe was referenced). Nicotine taken in smoking doses thus seems to be relatively safe for healthy adults to use, and stands in marked contrast to the deleterious short-term and long-term consequences of the socially acceptable substance, alcohol. Without tolerance to the desired effects, smokers do not have to keep on increasing the dose of nicotine to achieve the desired amount of stimulation or sedation. Evidence for chronic toxicity due to nicotine alone, rather than cigarette smoke, is sparse; and there is little convincing evidence of intellectual impairment even after a lifetime of use.

muscle disease paper.

Not aware if nicotine alone not available.

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10. Nicotine and Future Product Design

A number of important implications follow from these facts about nicotine. If smokers derive beneficial effects from nicotine, and cigarettes are the most effective method of administering nicotine, then cigarettes should be designed to deliver nicotine and its beneficial effects with minimum risk. The current trend of continuing to reduce nicotine, as well as 'tar' and carbon monoxide, cannot have the expected health benefits because smokers are compensating by puffing harder and inhaling more smoke. A more effective approach for minimising risk and maximising benefit would be a product with medium nicotine delivery but a reduction of some smoke components. For this strategy to be successful, it is obviously crucial that the cigarette has sufficient flavour. The reductions of smoke yield have been unsatisfactory so far because they remove important flavours. Future progress must be in the direction of reduction of specific smoke constituents to reduce risk but maintaining flavour by adding flavouring in order to preserve the characteristic full flavour impact for the smoker.

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