Symposia

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Neurobiology of nicotine dependence

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The main dependence-related properties of nicotine are an ability to produce recognisable psychoactive effects (nicotine discrimination), to act as a positive reinforcer of behaviour (nicotine self-administration and dose-titration) and to produce neuroadaptations on repeated administration (nicotine tolerance and withdrawal). These experimentally-demonstrated phenomena support findings from field studies indicating the compulsive nature of tobacco use and resemble events underlying dependence on classical abused drugs. Neurobiologically, nicotine dependence originates with activation of neuronal nicotinic receptors, pentameric ligand-gated ion channels whose diversity of subtypes is matched by nicotine's broad spectrum of behavioural effects. Rodent research has attempted to define nicotinic receptor subtypes that trigger the development of dependence. Initial studies found a correlation between the potency of nicotinic agonists in nicotine discrimination in rats and in binding to putative high-affinity nicotinic receptors. This binding site was primarily a marker for heteromeric nicotinic alpha4beta2 receptors and it was proposed that they were responsible for nicotine discrimination. Effects of nicotinic agonists in the discrimination procedure and on rates of lever-pressing and locomotor activity were dissociable, suggesting that different nicotinic receptor subtypes were involved. Antagonists acting at heteromeric nicotinic receptors readily antagonised many behavioural effects of nicotine, but depressant effects on locomotion and lever-pressing were blocked less readily. In contrast, an antagonist that acts mainly at homomeric alpha7 receptors did not block any behavioural effects. The experiments with agonists and antagonists therefore suggested that alpha4beta2 rather than alpha7 receptors were involved in nicotine dependence, but they did not distinguish between alpha4beta2 and several other heteromeric receptor subtypes. Recent studies with 'knockout' mice supported the alpha4beta2 hypothesis by showing that beta2-containing receptors were essential for nicotine discrimination. The impact of beta2 gene deletion on other behavioural effects including nicotine tolerance was variable, confirming their mediation by differing receptor subtypes. The mutually supportive findings with classical pharmacological and molecular-biological techniques strengthens knowledge underlying development of pharmacological aids to smoking cessation (supported by MRC).

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Past and future tobacco mortality

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In developed countries such as the United States, where cigarette smoking has been widely prevalent for many decades, tobacco is now responsible for about one-third of all cancer deaths, including 90% of the lung cancer deaths and 10–15% of other cancer deaths. In middle age the proportions are even higher, with tobacco accounting for half of all male and a quarter of all female US cancer deaths below age 70. The age-standardised cancer death rate from tobacco in the US has reached its peak in men but is still increasing in women. (There is no good evidence for any substantial increase in US cancer mortality rates during the past few decades over and above the changes that could plausibly be attributed to tobacco.) In addition, tobacco kills even more people by other diseases than by cancer, and is now responsible for about one-third of all US deaths in middle age.

Elsewhere, the epidemic is generally at an earlier stage, but is evolving. For example, current male mortality from tobacco is only three-quarters as great in Spain or Portugal as in the US, but is still increasing rapidly. Among Spanish and Portuguese women a strange situation exists. Few older women are lifelong cigarette smokers, so at present few are dying from the effects of tobacco. Nowadays, however, about half of the young women are cigarette smokers, and if they persist in the habit then about half will eventually be killed by it. Thus, although the epidemic of deaths from tobacco may soon be approaching its maximum in men, it is only just beginning in Spanish and Portuguese women.

A billion people now smoke worldwide, and hundreds of millions of them will be killed by their habit. About half of all persistent cigarette smokers are eventually killed by smoking, but stopping works remarkably well. Even in middle age, those who stop before they have lung cancer or some other serious disease avoid most of their subsequent risk of death from tobacco, and for those who stop before middle age the benefits are even greater.

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The smoking epidemic

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Every physician knows (or should know) that tobacco is, by far, the most serious genotoxic agent in the human environment, that it causes one-fifth to one-tenth of premature deaths in the various industrialized countries, and about one-fourth to one-third of cancers. Yet general practitioners and oncologists do not fight against smoking with all the vigor that is required. For example, many of them do not systematically question their patients about their smoking habits (whatever the cause of their consultation) and do not advise them to stop smoking, despite the effectiveness of this simple remark. Physicians should be much more convincing in promoting smoking cessation.

Two main problems will be considered: (1) Smoking among teenagers, since the earlier adolescents start smoking, the stronger will be their addiction, making smoking cessation more difficult. (2) Smoking during pregnancy, which is associated with serious health effects on the fetus and the newborn. Passive smoking can be a cause of serious infections of the upper respiratory tract and sudden death in infants and young children.

Smoking is certainly the main health problem in both industrialized and developing countries. Strategies have to be built for discouraging youngsters from starting smoking and inciting adults to quit smoking. But this is a difficult endeavor. Cigarettes have been strongly and effectively promoted over a century by advertising campaigns whose cost has amounted to billions of dollars and which were designed by the best but also the less scrupulous publicists and psychologists. The fight against smoking requires courage and energy in order to mobilize the whole medical community, teachers, politicians and the whole public. The various facets of this strategy will be discussed. Oncologists have a key role to play and they should be closely involved in this fight which appears to be the most promising way to reduce the cancer death rate during the 21st century.

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The economics and politics of tobacco

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Progress against tobacco has been seriously slow, given the mortality and morbidity of tobacco associated disease. While public health policy has been clear and substantially agreed since the early sixties, evolution of policies into law, which is necessary, has been slow because of the political inertia shown by every parliament in the world with the exception of Norway, Finland and Singapore. This political failure can only be explained by the existence of variable degrees of political corruption, which are underpinned and facilitated by arguments provided, worldwide, by the tobacco industry. The industry arguments are invariably based on economic considerations, and specifically not on health issues.

This presentation will compare the economic, political and public health arguments surrounding the key items of tobacco control policy, focussing on the relatively few areas where the economic facts are in real conflict with public health, as well as those where the two are in harmony.

In summary, there are very few real conflicts between economic truths and public health policy and there can be little argument that public health should be the dominant interest.