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DISCUSSION DOCUMENT

SMOKING AND HEALTH: FUTURE STRATEGIES FOR RESEARCH

1. EPIDEMIOLOGICAL APPROACHES

(i) Lung Cancer

Research claiming that smoking is associated with lung cancer

- Further research on this topic is unlikely to be a high priority for the scientific community except to study the associations between low tar products and disease. In order to be of use, such studies would have to study a generation who had smoked only low tar products. It would also be necessary in drawing comparisons with previous generations of smokers, to control for additional factors that may have changed in this generation e.g. dietary habits.

It is arguable that the tobacco industry should be carrying out such research. However, this is a very long-term project (answers could not realistically be expected for 25 years) and it is likely that, by then, the product may have changed significantly. The results may not therefore be directly relevant to the product of the future. In any case, a number of such studies are known to be already in progress e.g. funded by the ICSH in the UK.

Other factors associated with lung cancer

- Such studies have limited value. The list of factors associated with lung cancer is now extremely long. However, it does not directly address the association between smoking and lung cancer unless it could be shown that one or more of these factors are confounding factors e.g. all smokers who

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develop lung cancer are pet bird keepers or are exposed to diesel exhaust. Such research does, of course, serve to combat suggestions that smoking is responsible for 90% or more of all lung cancer deaths and resulting publicity may draw attention to the fact that smoking is not the only, nor even the major factor claimed to be associated with certain diseases.

Trends in disease and in cigarette smoking

- It has been noted by a number of scientists (e.g. Peter Lee using cohort analysis) that there is frequently a poor correlation between the trends in a disease such as lung cancer in the population, and patterns of cigarette smoking. As above the value of such studies is that they can point to the relative importance of other factors in the disease e.g. environmental factors. Unfortunately, the studies are unlikely to achieve more than to point out that anomalies exist and suggest they are due to other factors; the identification of which other factors is unlikely to be feasible. It is also impossible, because of inadequate death certificate information, to know whether changes in disease rates are different in smokers and non-smokers.

Trends in lung cancer subtypes

- A number of studies have now been published suggesting that lung cancer rates are increasing in non-smokers relative to smokers. This is frequently linked to a selective increase in lung cancer subtypes that have been found to occur less frequently in smokers e.g. adenocarcinoma. It would be useful to investigate this trend further.

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(ii) Cardiovascular disease

Research claiming that smoking is associated with cardiovascular disease

- Studies are still appearing on this subject, investigating the various subtypes of cardiovascular disease. In general, risk ratios e.g. (averaging 2 - 3 for coronary heart disease) are low enough for many such results to fall into the category of 'low risk epidemiology' and therefore to be subject to the associated problems.
- Atherosclerosis underlies many of the cardiovascular diseases that are claimed to be associated with smoking, and is also relevant to peripheral vascular disease. Particular attention should therefore be paid to literature relating to atherosclerosis when evaluating the claimed association between smoking and heart disease. It is noteworthy that the SRG is currently supporting work in the area of mechanisms of atherosclerosis, with Professor Kakkar at King's College London.
- Intervention studies (e.g. MRFIT) have shown that if individuals stop or reduce smoking there is no benefit in terms of a reduction in heart disease risk.

Other factors associated with heart disease

- Approximately 245 different factors have been claimed to be associated with heart disease. It would therefore be inappropriate to have such studies high on a list of priorities.

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- Diet has long been suspected to be a major risk factor associated with coronary heart disease; however, recently Professor Michael Oliver of Edinburgh University suggested that it could be a confounding factor in studies claiming an association between smoking and heart disease. He suggested that the claimed increased risk in smokers was not a direct effect of smoking, but an indirect result of smokers having a poor diet. Such work is certainly worth further investigation.

(iii) Respiratory disease

Research claiming that smoking is associated with increased risk of bronchitis and emphysema

- It is frequently stated that only smokers develop severe emphysema; this claim is worthy of further investigation. It is certainly not the case for bronchitis.

Other factors associated with respiratory disease

- A large amount of research has suggested other factors that have been associated with both bronchitis and emphysema. Again, there is probably little direct value in giving high priority to this kind of research.

(iv) Other diseases

- A number of other cancers and diseases have been claimed to be associated with smoking. For most of these, authorities such as the US Surgeon General accept that the evidence is insufficient to determine that a causal relationship exists. For other cancers, however, a causal relationship

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has also been suggested e.g. laryngeal, oesophageal and oral cancers. The majority of industry-funded work has tended to concentrate on lung cancer and therefore relatively little attention has been paid to anomalies in the literature relating to other cancers. It would be useful to pay a little more attention to these diseases in future.

EPIDEMIOLOGY: IMPLICATIONS FOR RESEARCH

High priority research

- Trends in lung cancer subtypes. It would be useful to commission a review considering whether the dissociation between adenocarcinoma and squamous and small cell carcinomas (in terms of their association with smoking) is a distinct one. From this, for example, it may be suggested that surveys should be carried out in key countries to provide more information about the relative incidence of lung cancer in smokers and non-smokers, and associated subtypes.
- Diet and heart disease, in particular relation to diet as a confounding factor in the association between smoking and heart disease. Michael Oliver could be approached as an initial step.
- Is it the case that only smokers develop severe emphysema? - A consultant's opinion could be obtained as an initial step.

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Low priority research

- Trends in disease in relation to cigarette smoking habits.
- Research into other factors in smoking-associated diseases e.g. pet birds.
- Long-term epidemiological studies into the effects of changes in the product.

2. MOLECULAR BIOLOGY/MECHANISMS OF DISEASE

Lung Cancer

- The most informative study in this area would be to identify a genetic factor that increases the risk of lung cancer, and to investigate whether incidence of the particular factor is different in smokers and non-smokers. Idle's work on metabolism of procarcinogens has so far covered the first part of this question, but has not yet adequately covered the second. However, before additional funding were to be committed, some additional questions need to be answered e.g. do the enzymes that Idle is interested in metabolise chemicals that may be relevant to the development of lung cancer?
- An alternative approach comes from Dr Helmut Bartsch from the IARC in Lyon. Dr Bartsch is investigating the relevance of P-450 systems in animals, which may shed some light on Professor Idle's research. They have also carried out work in smokers investigating the activity of such enzyme systems, which appear to be induced during smoking. Further research of this kind would complement Professor Idle's work, and possibilities are currently being discussed with Dr Bartsch.

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- A large amount of attention (both scientific and media) has been paid to the formation of DNA adducts for chemicals that occur in cigarette smoke. It is frequently assumed that this might have some bearing on carcinogenesis. However, this is by no means certain, and a recent review by Ashby (1988) suggests that care must be taken in application of tests based on such measures. It may not be appropriate to actually carry out research in this area if the relevance is in total doubt, however, Dr. Peter Farmer, Dr. Bartsch and Professor Bruce Ames are potential contacts in this area.

- Immunology is another area that is increasing in importance. For smoking, it has so far been relevant in two different areas: (i) respiratory disease and (ii) cervical cancer.
 - (i) A number of studies have claimed that smoking affects immune components of the respiratory system e.g. alveolar macrophage activity. The relevance of such studies is not totally clear but it has been suggested that a reduction in immune capacity would render an individual susceptible to disease and possibly even to the development of cancer. It would be extremely useful to have a review of this area to assess the potential need for further research in the field of immunology.

 - (ii) A study recently suggested that Langerhans cells, a component of the immune system, were reduced in the cervix of smokers. It was claimed that this reduced immune activity would make individuals more susceptible to viruses that may be associated with cervical cancer. However, Langerhans cells are just one component of the immune system; others were not studied. Again, a review would be useful leading to further research if necessary.

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Heart Disease

- It is frequently claimed in the scientific literature that smoking raises blood lipid levels and affects clotting. It would be useful to have someone review this area in order to analyse the evidence and determine whether more research would be useful.

Biological testing for carcinogenesis

- An extremely large number of recent reviews on the subject of carcinogenicity testing have cautioned that extreme care must be taken when extrapolating from in vitro and in vivo genotoxicity tests to human carcinogenesis. The relevance of such tests is not as yet established. Similarly, the appropriateness of other non-genotoxic animal models of carcinogenesis to the human situation has been questioned. Bearing this in mind, there would seem to be no particular value in spending a great deal of effort in developing new tests until such time as their relevance and the appropriateness of the model is more clear. The exception to this, of course, is that where regulatory authorities recommend the use of specific tests for the purposes of testing novel or modified products, when we should ensure that we have the capacity to carry them out.

High priority research

- Genetic differences that may influence the risk of lung cancer. Already being carried out with Professor Idle, and approaches made to Dr Bartsch at IARC.
- A review of immunology as it relates to smoking-associated diseases e.g. respiratory disease and cervical cancer.
- A review of the claimed effects of smoking on factors that may be relevant to heart disease.

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Low priority research

- Research related to the formation of DNA adducts, until such time as its relevance to carcinogenesis is more clear.
- Detailed research into novel animal models of carcinogenesis, including both in vitro and in vivo studies, except where recommended by regulatory authorities.

3. ENVIRONMENTAL TOBACCO SMOKE

(i) Epidemiology

- With the majority of studies (17 out of 23, with all their flaws) showing no statistically significant effect, there is little justification for carrying out others.
- Studies of potential confounding factors in epidemiological studies would be very useful. Although Peter Lee is still very enthusiastic about misclassification, it is not gaining particularly wide acceptance as a critical factor. Further studies in this area are unlikely to be of value (there are already several). It would be more useful to concentrate on other factors such as diet; this is currently being investigated in Hong Kong, e.g. by Linda Koo.
- The majority of studies have not shown a significant association between ETS and heart disease; however, there are some studies showing a significant association between ETS and the development of respiratory effects in small children. Further analysis of these studies would be useful, along with some research into potential confounding factors.

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(ii) Indoor Air Quality

- Research into sick building syndrome has established that ETS is not a significant factor. It is unlikely to be useful to carry out further research in this area unless required for specific purposes, e.g. in countries where such studies have not previously been carried out.
- We now have (thanks particularly to the Southampton ETS programme) a large body of data indicating that ETS is present in extremely low levels in a large variety of indoor situations. Future research in this area should probably now be restricted to studies that are useful for particular purposes e.g. to fight an airline ban on smoking; or in countries where ETS is just emerging as a problem, to give a local example of the kinds of levels of ETS that may be present in the air. For example, it has been suggested that there has been little investigation of ETS levels in the workplace in the USA.
- Research into indoor environments in warm climates has been relatively neglected, and it may be useful to carry out a study in such a country. This is currently being investigated with Covington & Burling in the Far East.
- Further investigation into the correlation between measures of nicotine levels in the air and measures of nicotine levels in saliva would be useful to address Martin Jarvis' work in children, which claims that they have very high cotinine levels in saliva if their parents are smokers.

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(iii) Chemistry of ETS

- Volatile organics in the air maybe of importance, particularly since the EEC are concentrating upon them. It would be useful to have more information about levels in the air.
- Aldehydes are major constituents of ETS: it might therefore be useful to know more about their concentrations and behaviour.
- Information about levels and behaviour of "other noxae" in ETS would be useful if it were possible to measure them.

High priority research

- Further research into confounding factors in epidemiological studies relating to ETS e.g. diet.
- Analysis of studies claiming to show respiratory effects of ETS in small children, with a view to further research into e.g. confounding factors.
- Research into levels of ETS components in buildings that will serve a particular purpose e.g. to combat a ban in a particular country. The ETS group in Southampton should be available to do this.
- Research into levels of ETS in buildings in warm climates e.g. Far East or Central America. Currently being investigated with Covington & Burling, and in Costa Rica.
- Further investigation into the correlation between measures of nicotine levels in air and in saliva. Currently underway by Chris Proctor.
- Research (where possible) into levels of "Other Noxae" in ETS.

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Low priority research

- Studies of misclassification.
- Research into sick building syndrome.
- Non-targeted research into levels of ETS components in air.

4. THE EFFECTS OF NICOTINE

(i) Addiction

- It is difficult to identify research areas that will have a bearing on the subject of whether or not nicotine is addictive. There is already some evidence indicating differences between nicotine and drugs that are generally accepted to be addictive, from both human and animal studies. Any additional evidence in this category would be useful but it should be borne in mind that even amongst the drugs that are accepted to be addictive there are differences.
- Work on alternative theories or explanations for why people smoke would be more constructive. To date, David Warburton has been something of a lone voice on the suggestion that smokers smoke, not because they are addicted, but because smoking fulfils a useful function for them. An analysis of the validity of Warburton's claims and further, more detailed work in this area is already going on at the University of Leeds.

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- It is extremely difficult to identify research into biological mechanisms of addiction, since it is not clear what they actually are. However, BAT is already supporting work in this area with Dr Roy Wise in Montreal, looking at effects of nicotine compared to other drugs in brain pathways and behavioural systems relating to reward and dependence.

(ii) Other effects

- Since there are a number of scientists who agree that nicotine has no carcinogenic or cardiotoxic effects, research in this area should have low priority.
- Effects of nicotine in situations of stress, anxiety, and on mood and performance are all relevant to the addiction question and therefore worthy of support. Work in this area is already planned at the University of Leeds.

5. PRODUCT MODIFICATION AND INNOVATION

To date, scientific evidence concerning specific components of cigarette smoke does not easily form a firm basis for the removal of specific compounds from cigarette smoke. Many of the animal models in which these compounds have been tested have little relevance to the development of cancer of the lung. However, in spite of this, bodies such as the IARC and regulatory authorities around the world have issued lists of compounds that they believe to be particularly problematic in relation to cigarette smoke.

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From a pragmatic point of view, because the scientific evidence is not conclusive, and because these regulatory authorities would themselves need to approve any significant product modification or innovation, the most sensible approach for BAT to adopt would be to follow their recommendations as far as possible. The following areas have been considered by regulatory authorities:

1. Lower Tar i.e. non-specific reduction of all smoke components. It is generally believed that, in markets such as the UK, tar has now been reduced to the limit in terms of consumer acceptability. Regulatory authorities such as the ICSH have therefore suggested that the tar:nicotine ratio of the product be altered such that lower tar does not result in lower nicotine. This, of course, assumes that nicotine is the most crucial component of cigarette smoke. Work in this area is conflicting but the overall consensus has been that the nicotine level that smokers generally take in is 0.8 mg per cigarette. The recommendation also assumes that nicotine is an acceptable (in "health" terms) component of cigarette smoke. Such an approach is certainly valid and Rothmans are also known to favour it.
2. Reduction in specific components. This has been considered in detail by BAT in the "Other Noxae" list, and a similar approach was adopted by RJ Reynolds in relation to "Premier". In any product modification or innovation, reduction or removal of these compounds should have priority.
3. Nicotine. It is generally accepted that nicotine is not genotoxic, carcinogenic or teratogenic. Although Hoffman and his group have assumed that nitrosamines formed from nicotine may be carcinogenic, this idea has not received widespread scientific acceptance. For cardiovascular disease, many scientists agree that nicotine is not cardiotoxic. Such effects as nicotine can be

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seen to have on the cardiovascular system are acute and not significantly different from the effects of mild exercise. The major area of scientific controversy relating to nicotine is whether it is addictive. However, the US Surgeon-General's Report made surprisingly little impact except amongst anti-smoking groups and the criticisms that have been made of it e.g. by David Warburton are valid and acceptable to many scientists. Except for the problem of the "image" of nicotine (it is a drug; without it, is would be difficult to argue that smoking is addictive) there is presently no justification for its removal. Nevertheless, we do not want a product based on nicotine alone; the pharmaceutical companies are covering this field quite adequately.

Philip Morris, however, have taken a different approach and introduced a nicotine-free cigarette. It will be interesting to see whether or not this is acceptable to the consumer.

4. Sidestream smoke. Regardless of conflicting research results relating to the claimed effects of ETS, regulatory authorities have reduction of sidestream as a priority. This should be a priority of BAT for aesthetic reasons, even if its reduction for health reasons is not justifiable. Regardless of the health issue, many people would like to see smoking banned because they find it is unpleasant and an irritant. Reduction of sidestream smoke is therefore a critical response. It would be particularly useful to decrease visible sidestream.

Testing of product modification or innovations

This area has been considered in some detail by the SRG in relation to RJR's launch of 'Premier' and the projects currently being undertaken by the BAT group. During the SRG's review process it was suggested that the comprehensive approach of RJR had perhaps set something of a precedent, and that it would probably be necessary for future products to be subjected to an equally exhaustive battery of tests.

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The most critical area to consider is on what grounds, i.e. on the basis of what tests, would a regulatory authority be prepared to concede that a particular new product might provide some kind of advantage over existing products?

In their various reports and discussions, regulatory authorities have considered the aspects of tobacco products discussed above (lower tar, reduction of specific components, the role of nicotine and the presence of sidestream smoke). It would be necessary to have a regulatory authority concede that a company had followed its recommendations in producing a novel product; if it did so then by definition it would have to concede that such a product must constitute an improvement over existing products. Presumably then, for example, the UK Independent Scientific Committee on Smoking and Health would have to concede by its own criteria that a product that had lower "tar", lower specifically identified chemicals and lower sidestream, would represent an improvement over current products.

Complications, of course, arise if, in modifying the product or introducing a totally novel product, new constituents are used and different chemicals are produced. It would then be necessary, as far as possible, to determine that these novel constituents did not have effects that could be interpreted as toxic. This is the process that was undergone by R. J. Reynolds in relation to glycerol as a major constituent of 'Premier'. A list of biological tests that the SRG considered that regulatory authorities would wish to see carried out is appended.

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