birthweight, a heavy environmental exposure to tobacco having comparable effects to those of a low 'active' consumption.

Moreover, the behavior of pregnant women smokers is influenced by the attitude of other smokers living in their surroundings. They are thus more liable to quit smoking during pregnancy if their partners adopt a similar behavioral change.

'Active' smoking during pregnancy, exposure of the child to environmental tobacco smoke and the child's development

This problem raises a major methodological difficulty, which is to distinguish between the effects of tobacco use by the mother during pregnancy, and those of environmental tobacco smoke released by either parent after the child's birth ('passive' smoking of the child). For instance, most women who smoke during pregnancy continue to do so after giving birth, whereas the majority of those who stopped smoking during their pregnancy resume with this habit once that they have given birth. In addition, many postnatal factors intervene in the child's health and development, so that it is very difficult to control for all of them in a single study.

There is some evidence suggesting that maternal smoking has an impact on the lung function of the child, but there is no evidence concerning a possible link between prenatal exposure to maternal smoking and an excess risk of childhood cancer.

On the other hand, a higher risk of unexplained sudden infant death has been found for babies whose mothers smoked, the risk rising as the level of tobacco consumption increases. However, neither the social characteristics differences that distinguish smokers from non-smokers, nor the lower birthweight in babies born to smokers can totally account for the excess risk, the latter also varying according to whether only the father, only the mother, or both parents smoke. While the role of tobacco in the sudden infant death syndrome is now well established, it is still not possible to determine the respective roles of intra-uterine exposure and postnatal exposure to tobacco smoke.

The potential consequences of maternal smoking on the psychomotor and the mental development of the child is another issue that remains to be solved. Several hypotheses on the mechanisms by which tobacco smoke can affect the fetal central nervous system *in utero* have been proposed. The epidemiological data remain controversial, although some of the reported inconsistencies may partially be explained by insufficient control for confounding factors in the studies carried out so far. These include maternal alcohol consumption during pregnancy, social characteristics and family stimulation of the child. In our present state of knowledge, it is not possible to draw definitive conclusions on whether or not smoking during pregnancy (or early childhood

Tobacco use by pregnant women

Over the past decades, the increase that has been noted in the proportion of pregnant women smokers in fact reflects a similar trend in the proportion of women smokers in the general population. For instance in France, whereas only 10% of pregnant women smoked in 1972, the figure rose to 17% in 1981, reaching 25% in 1995. However, about 40% of women smokers quit smoking during pregnancy, this proportion having remained stable across the years. Those who quit usually belong to more privileged social classes, and tend to be lighter smokers. They also tend to suffer more often from nausea or distaste for tobacco during pregnancy and usually live in an environment where there are less smokers.

'Active' smoking during pregnancy and the child's condition at birth

It is clearly established that smoking during pregnancy affects fetal growth, resulting in both lower birthweight and smaller size at birth. The birthweight deficit among babies born to smokers ranges between 150 g and 300 g when compared to newborns of non smokers, and correlates quite well with the level of cigarettes consumption during pregnancy. Even a modest daily consumption of less than 5 cigarettes can produce such an effect. The slightly shorter length of gestation that has also been reported for the babies of smokers cannot account for the lower birthweight and smaller size observed. In fact, the differences persist even after controlling for the characteristics that usually distinguish smokers from non smokers. Thus, prenatal exposure to tobacco smoke has a direct effect on intra-uterine growth. As an illustration, when regular smokers stop smoking during pregnancy, their newborns have quite comparable characteristics to those of non smokers.

Studies dating from the 60's have suggested a higher risk of perinatal mortality for the newborns of smokers, contrasting with more recent studies where this association has not been found. This may be explained by the fact that perinatal mortality has dramatically decreased since the 60's, making it more difficult to demonstrate a small effect on this parameter.

'Passive' smoking during pregnancy and the condition of the child at birth

Considering the composition of the air inhaled in the vicinity of smokers, it seems reasonable to assume that the exposure of pregnant women to environmental smoke can affect the fetus. However, measuring this exposure is difficult and the different procedures used in this kind of evaluation may account for the inconsistency observed in the results obtained so far. Nonetheless, currently available evidence is in favor of such an association between 'passive smoking' and a lower

PASSIVE SMOKING AND CARDIO-VASCULAR DISEASES

Daniel Thomas

In the August 1992 issue of 'Circulation', the American Heart Association published an important report on passive smoking and cardiovascular diseases (Taylor *et al.*, 1992). Based on a review of the available literature, the authors of this paper asserted that subjects who have been exposed to passive smoking in their households are liable to approximately a 30% increase in the risk of dying from a cardiovascular disease, and that the risk could even be higher for those exposed to passive smoking in their workplace. On consideration of the study by Glantz and Parmley (Glantz and Parmley, 1991), they also estimated the number of annual cardiovascular-related deaths that are attributable to passive smoking at about 35000 to 40000 in the United States. It was thus already suggested since then, that passive smoking was a major preventable cause of cardiovascular diseases and related deaths, and therefore all measures aimed at protecting non-smokers from passive exposure to tobacco smoke should be promoted.

Even though subsequently published papers (Deanfield, 1996; Gidding *et al.*, 1994; Glantz, 1993; Glantz and Parmley, 1995, 1996; Kritz *et al.*, 1995; Steeland, 1992; Steeland *et al.*, 1996; Weiss, 1996; Wells, 1994; Whidden, 1993; 1995) have also implied a role for passive smoking in the incidence of cardiovascular diseases, other sources have tried to deny this eventuality, or at least, to minimize its importance (Lee, 1992; LeVois and Layard, 1995). However, it is hard to consider these contradictory conclusions as being totally impartial, having been put forward by consulting doctors either working for the tobacco industry (Lee, 1992), or else, having been mandated and paid by the said industry to carry out a specific study on the problem (LeVois and Layard, 1995). The situation calls for the most objective state of mind in approaching this subject.

In this paper, will be considered:

- firstly, the known facts which derive from experimental studies carried out on passive exposure to tobacco smoke both in animals and in humans, and which ascertain the plausibility of the noxious character of passive smoking

- and secondly, the results of epidemiological studies that are now available.

A. EXPERIMENTAL STUDIES

Practically all the biological, humoral, cellular et hemodynamic effects observed with active smoking have also been demonstrated experimentally with passive tobacco smoke exposure. The earliest data have been described in detail by Glantz and Parmley (Glantz and Parmley, 1991) and by Wells (Wells, 1994). More recently, other findings concerning, in particular the acute effects of passive smoking on the endothelial function (Brown *et al.*, 1993; Celermajer *et al.*, 1996;

exposure to environmental tobacco smoke) affects the psychomotor and mental development of the child.

Prevention during pregnancy and early childhood

Even if some questions remain unanswered, there is sufficient evidence to justify the need for improving preventive actions. Interventions carried out to date have shown limited efficacy in curbing women smokers' attitudes during pregnancy, and even less so after the birth of the child. However, there is room for other types of action involving not only the pregnant women, but also their partners, while insisting on the need of pursuing these actions after the child's birth.

- Experimental studies carried out on the chicken, the pigeon and the mouse have demonstrated that a carcinogenic agent such as benzo-alpha-pyrene can stimulate the growth of atherosclerosis deposits (Glantz and Parmley, 1991; Whidden, 1993). These results were confirmed more recently in studies on rabbits (Zhu *et al.*,1990; Sun *et al.*, 1993) and on cockerels (Penn and Snyder, 1993, 1996; Penn *et al.*, 1994).
- In humans, Howard *et al.* (1994) studied the evolution of the carotid wall intima-media thickness in approximately 13,000 men and women aged between 45 to 64 years, who were classified according to their status as smokers, ex-smokers, exposed non-smokers (passive smokers) and unexposed non-smokers. It was found that intima-media thickness was more important in passive smokers as compared to unexposed non-smokers. However, the difference was only significant ($p<0.0001$) among the younger subjects of the cohort. It is also interesting to note that the intima-media thickness in passive smokers was directly proportional to the intensity of the exposure measured in hours per week ($p=0.003$).
- The lipid profile is also affected, including in the younger subjects, as reported in several studies (Feldman *et al.*, 1991; Moskowitz *et al.*, 1990; Pomrehn *et al.*, 1990; White *et al.*, 1992), with in particular a significant decrease in HDL-cholesterol.

To sum up, there is enough experimental evidence, including data on humans, in favor of a possible role of passive smoking in accelerating the constitution of atherosclerosis plaques and in their related complications.

B. EPIDEMIOLOGICAL STUDIES

a) Wells' meta-analysis

This important meta-analysis of epidemiological studies was carried out in 1994 (Wells, 1994), covering the results of 12 studies which regrouped a total of 3131 cases (Butler, 1988; Dobson *et al.*, 1991; Garland *et al.*, 1985; He *et al.*, 1989, 1994; Hirayama, 1990; Hole *et al.*, 1989; Humble *et al.*, 1990; Jackson, 1989; Lee *et al.*, 1986; Sandler *et al.*, 1989; Svendsen *et al.*, 1987). Only 7 out of the 12 studies had a prospective design, the rest being case-control studies. None had specifically studied the acute effects of passive smoking, in the sense that no investigation was carried in order to find out whether a subject had been exposed to passive smoking during the hours immediately preceding his cardiac event. The relative cardiovascular mortality and morbidity risks have been estimated as follows:

- Relative cardiovascular morbidity risk in relation with passive smoking (Wells, 1994):
  - the relative risk for women (6 studies) has been estimated at 1.51, with a 95% confidence interval from 1.16 to 1.97.
  - the relative risk for men (4 studies) has been estimated at 1.28, with a 95% confidence interval between 0.91 and 1.81

Hutchinson *et al.*, 1996; Zhu and Parmley, 1995) as well as its chronic atherogenic effects (Diez-Roux *et al.*, 1995; Howard *et al.*, 1994; Penn *et al.*, 1994; Penn and Snyder, 1993, 1996; Roberts *et al.*, 1996) have become available.

a) Acute effects

By contrast with the carcinogenic effect of tobacco which is closely related with the duration of exposure, some cardiovascular effects are directly related to the acute effects of tobacco smoke. The following phenomenons observed with active smoking, have also been found during passive tobacco exposure:

- An increased platelet sensitivity for aggregation (Burghuber *et al.*, 1986; Davis *et al.*, 1989, 1990; Hung *et al.*, 1995; Sinzinger and Kefalidès, 1982; Sinzinger and Virgolini, 1989). In fact, a mere 20 minutes of passive exposure to tobacco can increase the platelet sensitivity by 60 to 80% (Burghuber *et al.*, 1986; Davis *et al.*, 1989, 1990; Sinzinger and Kefalides, 1982), although this effect is only temporary.
- A significant increase in the level of fibrinogen, which represents a thrombosis risk factor (Iso *et al.*, 1996)
- Arterial motricity dysfunction. It had already been shown that endothelium dependent vasodilatation is impaired in cigarette smokers, including in young people presenting no advanced arterial lesions (Zeiher *et al.*, 1995). Quite similar arterial vasomotor problems, as a result of endothelial functional impairment, have recently been demonstrated in passive smokers (Celermajer *et al.*, 1996), and to a relatively comparable extent to that observed in active smokers. It is known that such an endothelial impairment is one of the contributing factors in the constitution of atherosclerosis plaques.
- A decreased blood oxygen transport capacity, resulting directly from the presence of carbon monoxide in passive tobacco smoke (Dwyer and Turino, 1989). Exposure to passive smoking significantly raises carboxyhemoglobin concentrations, thus decreasing the oxygen transport capacity. In addition, experimental studies have revealed a reduced tolerance of the myocardium to ischemia under these circumstances (Van Jaasveld *et al.*, 1992; Zhu *et al.*, 1994)
- An increased heartbeat frequency, which translates into increased oxygen needs for the myocardium. This, in association with the lower oxygen transport capacity, results in a decreased exercise performance of the subject, both for those having coronary heart disease (Khalfen and Klockhov, 1987) and also for healthy young people (Leone *et al.*, 1991, McMurray *et al.*, 1985).

b) Chronic effects

- Exposure to passive smoking significantly increases the concentration of circulating fragments of endothelial cells (Glantz and Parmley, 1991) as a result of vascular endothelial lesions, thus promoting the constitution of atherosclerosis plaques.

relative risk being multiplied by 10 to 20), such a misclassification should only have a very slight effect (about 10 times less important) on a presumed overestimation of the risk.

- Confounding factors have not always been taken into account in these studies, especially the ones having the largest number of subjects. If age has always been adjusted for, hypertension and hypercholesterolemia were taken into consideration in only half of the studies, weight in just 5 studies out of 12, and diabetes in only one study. Considering the usually multifactorial character of coronary heart disease, this lack of adjustment may indeed represent a relatively important source of bias.
- The last bias usually mentioned refers to the possibility that certain studies are not published (Hunt *et al.*, 1986; Palmer *et al.*, 1988), the idea being that studies revealing negative results are usually not published. For instance, PN Lee points out the absence of any publication concerning the results of the first study carried out by the American Cancer Society on over 1 million subjects of both sexes. Only the results concerning passive smoking and lung cancer have been published in 1981, whereas no information was ever published concerning passive smoking and cardiovascular diseases (Lee, 1992).

It is understandable that such critics could, until recently, raise some doubts concerning the real impact of passive smoking on the occurrence of cardiovascular diseases.

c) The prospective Cancer Prevention Study II (CPS II) (Steenland *et al.*, 1996)

Since the meta-analysis of Wells, and apart from two other not very informative complementary studies (La Vecchia *et al.*, 1993; Muscat and Wynder, 1995), it was not until August 1996 that the subject was again debated following the publication in "Circulation" of the results of the prospective Cancer Prevention Study II of the American Cancer Society. This is the most important study published up to now, concerning a total of 353,180 female and 126,500 male never-smokers, who had been enrolled in 1982 and followed up prospectively until 1989. The published analysis was made on a cohort of 309,599 couples, this figure including 135,137 couples for whom information relative to the smoking or non-smoking status was directly obtained from both spouses (hence reducing the risk of misclassification bias to a minimum). 10% of all married men and 28% of married women were living with a smoker, whereas 10% of married men and 32% of married women were living with ex-smokers.

During the follow-up period, 1800 coronary-heart related deaths were recorded among the married couples. After adjusting for certain cardiovascular risk factors (age, education level, hypertension as declared by the subject, diabetes, antihypertensive treatment, alcohol consumption, diet, physical exercise, BMI), the following results were obtained:

- the relative coronary heart-related death risk for non-smoking men married to smokers was estimated at 1.22 (95% confidence interval from 1.07 to 1.40) as compared to those who were married to non-smokers.

- Relative cardiovascular mortality risk in relation with passive smoking (Wells, 1994):
  - the relative risk for women (7 studies) has been estimated at 1.23, with a 95% confidence interval from 1.11 to 1.36.
  - the relative risk for men (5 studies) has been estimated at 1.25, with a 95% confidence interval from 1.03 to 1.51
- A dose-response relation was found (Wells, 1994)
  - for the women in 3 out of 6 studies on morbidity, and in 5 out of 7 studies on mortality.
  - for the men in only one out of 4 studies on morbidity, and in 2 out of 5 studies on mortality.
- Adjusment for other cardiovascular risk factors. A detailed analysis of these different studies showed that the relative risk of passive smoking was, on average, less important in studies where the main cardiovascular risk factors had been adjusted for, although the confidence intervals were narrower and with a higher statistical significance (Wells, 1994).

Similarly to previous works by Glantz and Parmley (Glantz and Parmley, 1991) and by Steenland (Steenland, 1992), the author of this meta-analysis (Wells, 1994) has carried out a quantitative estimation of the absolute number of deaths that could be related to passive smoking. Considering the mean relative risk to be equal to 1.22 (obtained after a optimum adjustment for other cardiovascular risk factors), the number of annual deaths related with passive smoking would then be around 62,000 in the United States (approximately 33,000 women and 29,000 men) (Wells, 1994). These figures are even worse than what had previously been estimated (Glantz and Parmley, 1991; Steenland, 1992).

b) Critics of the methodology

Several critics, essentially coming from PN Lee (Lee, 1992), have been laid against the studies included in this meta-analysis. Even though, as we have already mentioned in the introductory paragraph, great caution must be taken regarding the objectiveness of this work carried out by a tobacco industry consultant, a certain number of remarks based upon an individual analysis of these studies deserve to be looked into more carefully:

- All the studies, except those by Sandler (Sandler *et al.*, 1989) and Hirayama (Hirayama, 1990), concern a very limited number of cases. Consequently, even though the relative risk attributable to passive smoking, especially with respect to mortality, was found to be increased in almost all the studies in a relatively consistent manner, the 95% confidence intervals were relatively large, the lower limit being often less than one. However, this lack of power was lessened in the meta-analysis taking into account all the studies (Wells, 1994).
- Another methodological critic pointed to the misclassification with respect to the active smoker status. However, given that the increased risk resulting from an active use of tobacco is less important for cardiovascular diseases (relative risk of 1.70) as compared with lung cancer (the

- no dose-response relationship was found between the relative risk and the intensity of exposure, but no such relationship was found in many other studies either (see above).

d) The latest meta-analysis by Law

A new meta-analysis based on 19 published studies, covering 6,600 ischemic heart disease events, appeared in the British Medical Journal of October 18th 1997 (Law *et al.*, 1997). The results are identical to those obtained in the former meta-analysis by Wells. The relative risk of ischemic heart disease associated with environmental tobacco smoke was thus estimated at 1.30 (1.22-1.38) at age 65 and was the same for both genders. After controlling for diet in the analysis, the relative risk estimate was equal to 1.23, which corresponds to exactly the same result as that given by Wells (Wells, 1994) and close to the value of 1.2 found in the CPS II cohort study by the American Cancer Society (Steenland, 1996).

The new information is that if we consider people of the same age, the relative risk of passive smoking (1.30) is more or less similar to that of smoking one cigarette a day (1.39), whereas for a daily consumption of 20 cigarettes, the risk has been evaluated at 1.78 (1.31-2.44). This shows that at low doses, the risk is more than proportional to the dose. The mechanism underlying this effect could be explained by the platelet aggregation as reproduced experimentally by exposure to ETS. The increase in the risk was then evaluated at 34%.

Conclusion

Currently available data concerning the cardiovascular risk in relation to passive smoking show that:

1) Numerous animal as well as human experimental data, have confirmed that passive smoking exposure causes hemodynamic, biological as well as arterial structure changes (endothelial function and alteration of the arterial walls) in ways, qualitatively and sometimes quantitatively, similar to those observed with active smoking. These data give credit to the plausibility of a cardiovascular risk in association with passive smoking exposure.

2) The global analysis of the epidemiological studies, including the last prospective recently published study (CPS II Cohort of the American Cancer Society) (Steenland *et al.*, 1996) demonstrates an increase in the relative risk of dying from a cardiovascular disease at about 1.2 (the meta-analysis by A.J. Wells which also takes into account the results of this study estimated the RR at 1.23 with a 95% confidence interval from 1.14 to 1.33) (the results of this meta-analysis have not been published but were briefly mentionned in the editorial by Glantz and Parmley (Glantz and Parmley, 1996).

- the relative coronary heart-related death risk for non-smoking women married to smokers was estimated at 1.1 (95% confidence interval from 0.96 to 1.27) as compared to those who were married to non-smokers.
- no significant difference in risk was noted for non-smoking subjects who were married to ex-smokers.
- an analysis carried out on a sub cohort of couples, for whom direct information concerning smoking status was individually obtained, did not give very different results: the RR being estimated at 1.23 (1.03 to 1.47) for men and at 1.19 (0.97 to 1.45) for women respectively.

The relevance of the information deriving from this study has been underlined in an editorial by Glantz and Parmley (Glantz and Parmley, 1996):

- by itself, this study has reported nearly as many deaths in relation to passive smoking as the 14 previously published studies taken together, with the further advantage of having a prospective study design.
- it puts a halt to the repeated critics relative to the absence of any publication concerning the results of the Cancer Prevention Study. It must be stated that LeVois and Layard (LeVois and Layard, 1995) had previously analyzed the results of this study in 1995, giving diverging conclusions, that is, namely the absence of any increase in the relative risk of dying from coronary-heart diseases. However in this analysis, the authors (mandated by tobacco industry lawyers) had used a different definition for the smoking status of the spouse, by considering even those who had stopped tobacco use prior to enrollment in the study as spouse smokers. Consequently, this introduced an important source of bias which probably explains the negative results obtained.
- it confirms the role of the acute effects of passive smoking as a component of the cardiovascular disease risk. Indeed, the analysis does not show any increase in the relative risk for subjects married to a person classified as an ex-smoker at the start of the study. This leads us to hypothesize that the cardiovascular risk of passive smoking (as in the case of active smoking) is largely linked with the acute effects of tobacco, especially the hemodynamic effects, the increased concentrations of carboxyhemoglobin and the impairment of the endothelial function, all these changes predisposing to risk of rupture of atherosclerosis plaques, and hence to acute thrombotic complications.

Nevertheless, several limitations have to be made concerning the results of the CPS-II study:

- no precise information concerning some very important cardiovascular risk factors were available, such as the lipid profile, the eventuality of cholesterol-lowering treatments and blood pressure measurements.

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3) Passive smoking-related mortality is essentially due to cardiovascular causes (about 70% of this mortality). Indeed, the increase in the relative risk of cardiovascular diseases in association with passive smoking is proportionately similar to that of lung cancer. However, given the higher prevalence of cardiovascular diseases, the absolute number of deaths from cardiovascular causes in association with passive smoking could be ten times as high as lung cancer-related deaths. The estimated annual figures for the United States range from 30,000 to 60,000 deaths, whereas Philip Whidden (Whidden, 1993) evaluated, perhaps exageratedly, at 97,000 the expected number of deaths in Europe, including 7,578 for France (vs. 735 deaths by lung cancer).

4) If the last study concerning the cohort of the American Cancer Society (Steenland *et al.*, 1996) has allowed to discard most of the critics raised in previously published studies, further more precise information can only be obtained from studies who will investigate into the following issues:

- measure objectively and precisely the intensity of passive smoking exposure

- take into consideration all possible exposure sources, and not only that represented by the spouse of the study subject

- set intermediary evaluation criteria such as the study of hemostasis, the lipid profile and the intima-media thickness of the carotid wall etc....

- take into consideration the main cardiovascular risk factors and quantifying precisely their magnitude in order to get absolutely rid of biases in relation with confounding factors.

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that environmental tobacco smoke could be causally associated with the occurrence of a disease, in particular lung cancer, among non-smokers. These assertions were based on only about twelve studies (of which two were cohort studies) regrouping a total of less than 1000 patients for the case-control studies.

Since then, twenty seven new studies, including three new cohort studies (Butler, 1988, Hole *et al.*, 1989; Cardenas *et al.*, 1997) have been published. This represents a total of 5095 cases of lung cancer in non smokers (4626 women, 274 men). In two studies, the results are given without distinction of gender (Hole *et al.*, 1989; Janerich *et al.*, 1990). In addition, the data collection phase of a European multicentric case-control study (to which France has largely contributed) has now been completed. The German data have appeared in the media, showing that prolonged high exposure to ETS at the workplace increases the cancer risk by a factor of 2 (Wichmann *et al.*, 1997). The studies with results showing a significant increase in the risk for non smoking women are summarized in table 1.

Such studies have however become increasingly complex to carry out over the years. This is due mainly to a more careful assessment of the real exposure to environmental tobacco smoke experienced by the subjects. For instance, in addition to the spouse's smoking, these studies have also taken into consideration other possible sources of exposure to ETS: in other circumstances (during childood, at the workplace, in public transportations, during leisure activities), with other persons (parents, other members of the family, work colleagues) and covering a longer period (Trédaniel *et al.*, 1994).

The study published under the supervision of Elisabeth Fontham (Fontham *et al.*, 1994) underlines the importance of exposure experienced during the childhood period. This survey, regrouping the highest number of patients known to date, revealed that the women who had been exposed during their childhood have a higher risk of developing lung cancer as compared to those who had experienced similar exposure conditions during adult life, but who had not been exposed as children. Hence, when considering the highest level of exposure during adult life, the relative risk estimate is equal to 3.25 (95% CI: 2.42-7.46) and 1.77 (95% CI: 0.98-3.19), respectively for women who had been exposed during their childhood as compared to those who had not.

Recently, it was found (Riboli *et al.*, 1995) that non-smoking women who had been exposed to parental smoking during their childhood were more likely to get married to someone who was a smoker than women whose parents did not smoke (OR=1.64; 95% CI: 1.21-2.17). Consequently, it appears that non-smoking women who are married to smokers have a higher probability of

PASSIVE SMOKING AND CARCINOGENIC RISK FOR THE LUNG

Jean Trédaniel

Passive smoking can be defined as the involuntary inhalation by a non-smoker of tobacco smoke released by one or several smokers in his/her immediate surroundings. Whereas the adverse effects of active smoking have been recognized since the nineteen fifties, twenty more years have been necessary for pediatricians to start to look into the possible harmful effects on health of environmental tobacco smoke.

Four arguments can be put forward, bringing us to raise the question of a potential carcinogenic role played by environmental smoke for the lung, thus warranting the conduct of epidemiological studies:

- it is well known that there has always been a small, but real fraction of patients with lung cancer in spite of the fact that they were non smokers. This specific population justifies the conduct of research on risk factors, other than active smoking, that are responsible for this cancer. Among the potential candidates as etiologic factors, the role played by environmental tobacco smoke deserves to be assessed;
- and this is even more justified, given that the chemical analysis of the different streams of tobacco smoke shows that the secondary stream (corresponding to what is yielded from the cigarette between puffs, constituting the major fraction of environmental smoke) contains, for an equal volume, higher concentrations of toxic substances, including carcinogens, resulting from the combustion of tobacco (IARC, 1986);
- finally, these different components of tobacco smoke have been found in the biological fluids of the passive smoker. These include not only urinary cotinine, the best known biological marker used to detect exposure to environmental smoke, but also carcinogenic compounds (Hecht *et al.*, 1993);
- given that no consensus exists on the threshold level, for the carcinogenic effect of tobacco smoke in the active smoker, studies are warranted in order to demonstrate how much the risk of lung cancer may be increased for the passive smoker.

It was not till 1981 that the results of the first studies carried on primary bronchial cancers among passive smokers were known (Hirayama, 1981; Trichopoulos *et al.*, 1981). In 1986, two American reports, one conducted by the administration of the Ministry of Health under the authority of the Surgeon General (US Department of Health and Human Services, 1986) and the other one by the National Academy of Sciences (National Research Council, 1986), have reached the conclusion

A remarkable meta-analysis of these studies has very recently been published in the British Medical Journal (Hackshaw *et al.*, 1997). The relative risk of lung cancer for women exposed to environmental tobacco smoke of their spouse has been estimated at 1.24 (CI 95%: 1.13-1.36; p<0.001). This result corresponds to a 24% increase in the risk of developping the disease for a non smoker exposed to environmental tobacco as compared to the 'inherent' risk in a real non smoker. A dose-response effect has been demonstrated. Thus, the risk increases by 23% (14 to 32%) for every 10 additionnal cigarettes smoked by the spouse. In addition, considering the studies relating only to men, or those where the gender was not specified, the outcome is unchanged (RR: 1.23; IC 95%: 1.13-1.34). Similarly, after controlling for the two before-mentionned biases (misclassification of the status with respect to tobacco use and the effect of dietary habits), the result is not changed, the excess risk having then been estimated at 26% (7 to 47%).

Even if the magnitude of the risk may appear small by comparison with the active smoker's risk at the individual level, the consequences at the level of a whole nation could be quite important considering the fact that the majority of the population is then concerned. As an illustration, a recent study revealed that 87.9% of all American adult non-smokers had measurable serum levels of cotinine showing that they had therefore been exposed to environmental tobacco smoke (Pirkle *et al.*, 1996). In a recent study carried out in the 15 countries of the European Union in 1990, the number of lung cancer-related deaths was estimated at 1146 (836 women and 307 men) observed in non-smokers that could be attributed to the spouse's smoking. The corresponding figures for France are estimated at 105 deaths (including 59 women and 46 men) (Trédaniel *et al.*, 1997) and at 400 for Germany (Beicher *et al.*, 1994). Given that those results have not taken into account other possible sources of exposure to environmental smoke (during childhood, at the workplace, in public transports, etc.), this is probably a big underestimation of the actual number of lung cancer deaths attributable to passive smoking. Similarly, the US Environmental Protection Agency (US Environmental Protection Agency, 1993) has estimated the annual number of such deaths at 3000 in the United States. All these data have led the American administration to declare involuntary tobacco exposure as a lung carcinogenic agent in the workplace (US National Institute for Occupational Safety and Health, 1991).

Considering the importance of the potential risk in the European countries, where the prevalence of active smoking among adults is still alarmingly high, this information provides a sound basis for the adoption of legislative measures that would consider environmental tobacco smoke as a potential carcinogenic agent, thus warranting the need for the protection of non-smokers in closed premises. The scientific debate is over. The results obtained over the last 16 years, which

having been exposed during their whole lifetime to environmental tobacco smoke. This is in agreement with the results previously obtained in studies which had shown an increased lung cancer risk even when only the spouse's smoking was taken into consideration, since parental smoking and spouse smoking are apparently correlated.

The bias which has been most under scrutiny concerns the status of ex-smokers or present smokers who have wrongly been classified in the passive smokers group. This misclassification results in an increased risk among passive smokers because the risk corresponding to some active smokers has been included in the estimation of the global risk. Several studies have looked into this problem. For instance, the International Agency for Research on Cancer (Riboli *et al.*, 1990) carried out such a study confirming that from 2 to 3% of the subjects who declared themselves as non-smokers were in fact active smokers. However, we have recently shown that this estimate is in fact probably lower (Riboli *et al.*, 1995). On the other hand, one must bear in mind the ubiquitous character of passive smoking, so that some non smokers are in fact passive smokers. In this case, we run the risk of underestimating the difference existing between the "true" non-smokers (if such people exist) and the passive smokers.

The question of bias linked to dietary habits also needs to be raised. Indeed, smokers tend to have a diet rich in fats and poor in fruits and vegetables, the latter being by itself correlated with an accrued risk of lung cancer. Non-smokers may also have this type of diet when they share the lives of smokers. In this case, the accrued lung cancer risk observed among these non-smokers could be attributed more to their poor dietary habits, than to their spouse's smoking. However, the studies which have adjusted their results for dietary habits have not been able to demonstrate this clearly. In any case, this question will be solved when enough results will become available (including those of the European study which is being analyzed) from studies concerning exposure experienced at the workplace, given that if one may suppose that two spouses share the same type of diet, this cannot be the case between work peers.

Several meta-analyses covering all the studies published so far since 1981 have been conducted. The results are summarized in table 2. All of them, save for the study by Fleiss, show a significantly increased relative risk which has globally been estimated at 1.3. The analysis carried out by the U.S. Environmental Protection Agency (US Environmental Protection Agency, 1993) gave highly significant results ($p<0.005$). But, in two regions, Western Europe and China, a statistically non significant increased risk was found.

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Table 1: Main characteristics and results of studies having shown a significant increase in the relative risk of lung cancer among non smoking women living with a smoker

Author	Year, Country	Cases	Controls	RR	95% CI
Trichopoulos	1983, Greece	62	190	2.13	1.19-3.83
Hirayama*	1984, Japan	200	91340	1.45	1.02-2.08
Lam	1985, Hong Kong	60	144	2.01	1.09-3.72
Lam	1987, Hong Kong	199	335	1.65	1.16-2.35
Geng	1988, China	54	93	2.16	1.08-4.29
Fontham	1994, USA	651	1253	1.26	1.04-1.54
Zaridze	1995, Russia	162	285	1.66	1.12-2.45

*cohort study

RR: relative risk

95% CI: 95% confidence interval

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PASSIVE SMOKING AND NON TUMORAL RESPIRATORY DISEASES IN ADULTS

Jean Trédaniel

Passive inhalation of tobacco smoke causes immediate irritation of the eye as well as the upper respiratory tract.

The question is whether there are long term adverse effects of passive smoking for the respiratory system. The results deriving from studies assessing this possible consequence are however much more difficult to appreciate than those dealing with the carcinogenic risk for the lung. The list of affections that could be concerned include all the various chronic obstructive diseases affecting the respiratory system (chronic bronchitis, emphysema, bronchial dilatation, to which we can also add asthma) which are not easily apprehended individually in the framework of epidemiological studies. However, we can draw several conclusions on reviewing the available literature (Trédaniel *et al.*, 1994):

- there is a strong biological plausibility between an exposure to environmental tobacco smoke and the affections concerning the respiratory tract,
- the respiratory functional tests, so long as they are elaborate enough to study the effects on the small respiratory airways (namely by tracing the flow-volume curve) reveal a statistically significant decrease in the air flow among passive smokers. However, the clinical and prognostic significance of these changes remain subject to caution,
- the earliest clinical studies have yielded inconsistent results which have led most investigators to doubt the existence of an association between passive smoking and non-tumoral respiratory diseases in adults. This opinion should however be taken with caution especially in the light of recent findings (Robbins *et al.*, 1993; Dayal *et al.*, 1994), including those from a European study (Leuenburger *et al.*, 1994), indicating that passive smoking in adult life can cause respiratory symptoms, and even be at the origin of chronic respiratory diseases (Leaderer and Samet, 1994).

Table 2: Results of meta-analysis carried out on the case-control studies, estimating the relative risk for the passive smoker of developping a primary bronchial cancer as compared to the non exposed non-smoker

AUTHOR (year)	RR	95% CI
NRC (1986)	1.34	1.18 - 1.53
Blot (1986)	1.3	1.1 - 1.5
Wald (1986)	1.35	1.19 - 1.54
Wells (1986)	1.44	1.26 - 1.66
Saracci (1989)	1.35	1.20 - 1.53
Zmirou (1990)	1.47	1.33 - 1.63
Fleiss (1991)	1.12	0.95 - 1.30
Tweedie (1992)	1.17	1.06 - 1.28
EPA (1993):		
- Greece	2.01	1.42 - 2.84*
- Hong-Kong	1.48	1.21 - 1.81*
- Japan	1.41	1.18 - 1.69*
- USA	1.19	1.04 - 1.35*
- Western Europe	1.17	0.84 - 1.62*
- China	0.95	0.81 - 1.12
Pershagen (1994):		
- Europe	1.47	1.12 - 1.92
- USA	1.23	1.02 - 1.49
- China	1.10	0.94 - 1.28
- Japan	1.32	1.08 - 1.61
- Global assessment	1.23	1.12 - 1.35
Hackshaw (1997)		
- Women	1.24	1.13-1.36
- Men	1.34	0.97-1.84

RR: Relative risk

95% CI: 95% Confidence Interval

*: 90% CI

PASSIVE SMOKING AND CANCER CONCERNING SITES OTHER THAN THE LUNG IN ADULTS AND CHILDREN

Jean Trédaniel

Active tobacco smoking is directly correlated not only with lung cancer but also with a certain number of tumoral processes concerning other sites (larynx, upper aero-digestive tract, esophagus, pancreas, bladder, kidney, stomach and uterine cervix). There is a possibility that the risk for non-smokers having been exposed to environmental smoke to develop these types of tumors may be close to that of 'light' smokers.

In addition, since the contamination process by tobacco smoke is different between the active smoker (who inhales the smoke voluntarily) and the passive smoker, the latter enduring the exposure while breathing in a natural way and deeply inhaling the environmental smoke (which contains, as we know, carcinogenic agents present in tobacco smoke) one can imagine that passive smoking could expose to a risk of developing tumors on sites other than those which are directly associated with active smoking.

In fact, scarce data coming from rather scattered sources are available on the subject in the literature (Trédaniel *et al.*, 1993). Several studies have assessed the risk of cancer of the bladder and the uterine cervix among passive smokers, but none has been able up to now, with the means that are available today, to establish, in a convincing manner, an association between these cancers and passive smoking. In the case of tumors that are not directly related to environmental tobacco smoke, studies have been carried out on cancers of facial sinuses and breast, cerebral tumors, as well as digestive tract cancers. On reviewing the literature, one can only advance the hypothesis (in particular because a dose-effect association has been found) that the cancers of the facial sinuses encountered in non-smokers may be related to environmental tobacco smoke. Moreover, the findings of a recent Swiss study are in favor of an association between passive smoking and breast cancer among non-smoking women (Morabia *et al.*, 1996).

The question of whether environmental exposure to tobacco has a carcinogenic effect in children has not been solved yet (Trédaniel *et al.*, 1994). The high incidence of blood cancers and central nervous system tumors in the infant may lead us to suppose that, in spite of the fact that available epidemiological studies do not allow any definitive conclusions on the subject, exposure of the fetus or the child to carcinogenic compounds, and namely carcinogenic agents contained in tobacco smoke, could play a role in the occurrence of these cancers. Moreover, one should not disregard the potential role of paternal smoking (which can provoke spermatomutagenesis) as a recent study has underlined (Sorahan *et al.*, 1997).

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THE TOBACCO INDUSTRY DISINFORMATION ON PASSIVE SMOKING

Pascal Mélihan-Cheinin

In the preparation of this chapter, we have been heavily indebted to that marvelously informative book, 'The Cigarette papers', by Professor Stanton Glantz and his colleagues. We trust that these friends will be pleased that we have found it necessary to resort to their text so often.

Introduction

The history of research into second-hand smoking has followed a parallel course to that into active smoking, especially in regard to the efforts by the tobacco industry to deny and obfuscate that research. The latest example of tobacco-industry disinformation, which compares the hazards of passive smoking with the 'risks' of drinking milk and eating biscuits, is as senseless as were the industry's denials of the adverse health effects of active smoking in the past decades. The cigarette industry's arguments and strategy, which will be reviewed in this chapter, remain very similar

1. The reasons for the tobacco industry's concern about ETS

During the 1970s, as scientific evidence of the hazards of ETS was beginning to accumulate, the movement for the non-smokers' rights emerged. Gradually, people became less tolerant of smoking in public places and in the workplace. Restrictions on tobacco use started to be imposed, both by governments and private businesses, first in North America before and then in Western Europe a few years later.

The tobacco industry was quick to recognize the need to counter this emerging shift in social attitudes towards smoking, particularly at work. The recent disclosure of internal tobacco-industry has enabled the scientific community and the public to obtain proof of the conspiracy to keep people confused about passive smoking [Glantz *et al.*, 1996; Hilts, 1996].

In 1978, the Roper Organization conducted a confidential study for the United States Tobacco Institute on the changing attitudes of the public towards smoking [Glantz *et al.*, 1996]. This report obtained by the Federal Trade Commission, and subsequently made public, stated: 'The anti-smoking forces' latest task, however - on the passive smoking issue - is another matter. What the smoker does to himself may be his business, but what the smoker does to the non-smoker is quite a different matter... This, we see as the most dangerous development yet to the viability of the tobacco industry that has yet occurred.'

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RECOMMENDATIONS

Exposure to environmental tobacco smoke (ETS) has three main adverse consequences:
- it causes discomfort to most nonsmokers because of the smell and irritant effects;
- it worsens certain chronic health conditions, such as chronic respiratory and heart diseases;
- it causes lung cancer, coronary heart diseases, upper respiratory tract infections in children, and its role in the sudden infant death syndrome has now been recognized.

In view of the available scientific evidence concerning the hazards of ETS and the high proportion of nonsmokers who are regularly exposed to ETS, we can confidently say that **secondhand smoke is currently the most important indoor air pollutant having a serious negative public health impact**. The right of nonsmokers not to be exposed to ETS deserves consideration and no effort should be spared in keeping them from being involuntarily exposed during their everyday activities.

It follows that in enclosed indoor premises, **smoking should only be tolerated in physically separated and independently ventilated areas**.

The ultimate objective should be a total ban on smoking in all indoor public places for three main reasons:
- to give maximum protection to nonsmokers;
- to protect smokers from being exposed to very high levels of ETS in designated areas;
- to save money that would otherwise be invested in building separate ventilated areas for smokers

MAGNITUDE OF THE PROBLEM

Before adopting tobacco control legislative measures, health organizations have to play an active role in raising public awareness about the adverse effects of ETS. Government authorities in the European Union should encourage research aimed at improving our knowledge about the hazards of ETS exposure and providing means that would prevent such exposure. Raising public awareness about "secondhand smoking" involves conducting surveys among the general public in the various European countries in order to evaluate people's attitudes towards smoking, their knowledge about ETS, as well as their state of awareness about nonsmokers' rights.

INFORMATION AND IMPLEMENTATION

In parallel with the implementation of tobacco-control related laws, information campaigns aimed at the public should be set up to explain the reasons underlying the adoption of such measures. Particular attention should be given to nonsmokers, concerning their rights and what they can do when regulations are violated. Nonsmokers represent the majority of people, but many remain reluctant about committing themselves in protecting their interests in this domain. The EU should also help the Eastern European governments to launch similar information campaigns about the hazards of ETS and nonsmokers' rights in their respective countries.

CHILDREN

Children deserve a special place in any rational prevention program against exposure to ETS. For instance, health education programs and information campaigns should be directed at smokers whose activities imply being in contact with children. Specific smoking cessation programs should be proposed to pregnant women, their partners, as well as people taking care of children. Similar actions should also be promoted in schools (including colleges, universities and residential schools) hospitals and health care establishments.

TRADE UNIONS

Considering the high levels of ETS exposure usually encountered in workplaces, trade unions should be involved in the initiative to protect employees from this health hazard in the workplace. Employers should also be made aware of these union activities.

Finally, it is necessary to adopt, implement and enforce legislative measures and regulations that defend nonsmokers' rights within the European Union.

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