SMOKING: A FACTOR PROMOTING ONSET AND PROGRESSION OF DIABETIC NEPHROPATHY

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SUMMARY - Although smoking was identified two decades ago as a factor promoting the onset and progression of nephropathy in Type 1 and then in Type 2 diabetes, its role has been largely neglected. More recently, it has been shown that smoking adversely affects renal haemodynamics and protein excretion even in subjects without renal disease. In addition, it impairs the prognosis for renal function in patients with non-diabetic renal disease. Recent studies have suggested the involvement of sympathetic activation, increased endothelin production, and impaired endothelial cell-dependent vasodilatation in the genesis of smoking-induced renal function impairment. Cessation of smoking apparently slows progression to renal failure, but the decision to stop smoking is difficult because of the high addictive potential of the habit. The challenge remains for diabetologists and nephrologists to motivate patients to stop smoking.

Key-words: diabetic nephropathy, smoking, sympathetic nervous system, endothelin, proteinuria, progression.

RÉSUMÉ - Le tabagisme: un facteur favorisant l’apparition et la progression de la néphropathie diabétique. Il y a 2 décennies, le tabagisme a été identifié d’abord dans le diabète de type 1 puis dans celui de type 2, comme un facteur d’émergence et de progression de la néphropathie, mais son importance a été négligée. Plus récemment, il a pu être montré que le tabagisme altère aussi l’hémodynamique rénale et l’excrétion protéique, même chez des sujets sans maladie rénale. De plus, il altère aussi le pronostic fonctionnel rénal chez des patients atteints de maladie rénale non diabétique. Des études récentes ont suggéré l’implication d’une activation sympathique, d’une production accrue d’endothéline et d’une altération de la vasodilatation dépendante des cellules endothéliales, dans la genèse de la progression de l’insuffisance rénale liée au tabagisme. L’arrêt du tabagisme réduit apparemment la progression de la détérioration rénale, mais cet arrêt est difficile à analyser du fait de la forte dépendance vis-à-vis du tabagisme. Cela demeure un "challenge" pour les diabétologues et les néphrologues de motiver les patients pour arrêter de fumer.

Mots-clés : néphropathie diabétique, tabagisme, système nerveux sympathique, endothéline, protéinurie, progression.

Since the seminal communication of Christiansen in 1978 [1], it has been known that cigarette smoking increases renal risk in diabetic patients. This early observation received little attention, and the impact of smoking on diabetic nephropathy has only recently been more widely assessed [2-4]. Such interest has been given a further boost by observations in patients with non-diabetic renal disease for whom increasing evidence points to smoking as a progression promotor [5-7]. Furthermore, new evidence has documented various pathomechanisms underlying the acute [8] and chronic [9] adverse effects of smoking on the kidney.

Although smoking should in principle be an avoidable renal risk factor, practical clinical experience is rather sobering [10], mainly because of the high addictive potential of cigarette smoking. Therefore, it may be appropriate to start with a brief recapitulation of the history of tobacco. The initial encounter of Europe with tobacco provides impressive evidence for the addictive nature of smoking. History can also help us understand the social and cultural forces underlying the current epidemic of cigarette smoking [11-15].

THE HISTORY OF TOBACCO

It is now considered that tobacco was unknown outside America before the voyages of Christopher Columbus. When Columbus landed on 15 October 1492, the natives offered a mysterious bunch of dried leaves as a present [16]. One month later, Rodríguez de Jerez was sent out for reconnaissance on what today is known as the island of Cuba. He reported on 14 November 1492 “that natives ignite dried leaves and inhale smoke”. This was rapidly confirmed by other observers. In his “Historia General y Natural de Las Indias”, Gonzalo Fernandez de Oviedo Valdez wrote in 1526 that “amongst other vices the Indians have the bad habit of inhaling some kind of smoke to become intoxicated.” They call it “tobacco” [17].

No more than 35 years after the voyages of Columbus, it was known that smoking caused addiction. Bartholome de las Casas wrote: “I saw several Spaniards on the island of Hispanola who were reproached because of their bad habits. They answered it was impossible for them to stop smoking” [18]. Ironically, when Rodrigo de Jerez, who had first encountered tobacco on the island of Cuba, returned to his native city of Ayamonte in Spain, the local population summoned the Holy Inquisition when they saw that he exhaled smoke from his mouth. Since this obviously had to be the work of the devil, he was thrown into jail and thus painfully weaned from smoking, which he promptly resumed when he was released many years later after smoking had become a widespread habit. The use of tobacco spread at a breathtaking pace. Within a few years it had reached Europe, and within one century the then known world.

It is unfortunate that the spread of tobacco was promoted at first by strong recommendations of physicians who extolled it as a panacea. Nicolò Monardas of Sevilla [19], one of the most respected Spanish physicians of his time, gave a rapturous description of tobacco’s medical properties, listing a number of indications (such as cough, asthma, headache, gastric pain, gout, women’s diseases and cancer), but he also correctly stated that tobacco alleviated hunger and thirst. It is only with amusement that we read today the statement of Van Peima in 1690 that “pregnant women should smoke as they cannot properly nourish the foetus if the stomach is not working...tobacco smoke stimulates the stomach” [20]. Such recommendations by physicians are not a page of glory in the annals of medicine since they bestowed respectibility on tobacco.

The spread of tobacco from the Iberian peninsula to France is related to its medicinal use. In the early 16th century, tobacco was cultivated as a decorative plant and medicinal herb in the gardens of the nobility at the court of Lisbon. Tobacco was thus widely known when Jean Nicot from Nimes arrived as the French ambassadord to the court of Lisbon. He sent seeds and plants to the Queen Mother Catherina de Medici at the French court. As Nicot (Fig. 1) had promulgated the tobacco plant as a medicinal herb and panacea, the name “Nicotiana” was adopted as the plant’s botanical name and the plant alkaloid was later called Nicotine.
The high hopes for the medicinal properties of tobacco soon proved disappointing, but the plant quickly became a commodity for the masses. As a result, the use of tobacco (mostly in the form of pipe smoking, chewing and snuffing) spread rapidly throughout Europe [16, 21].

Despite its great popularity, the consumption of tobacco per capita remained relatively low until the invention of the cigarette. Cigarettes originated in South and Central America and were known in Spain by the 18th century. Paper-wrapped tobacco, called papelate (after Spanish “papel” for paper) crossed into France in 1830, and in 1845 the French state tobacco monopoly began manufacturing them. They were not sold under the exotic name papelates, but under the name cigarettes, which sounded more French. However, they were not a commercial success in France. As often in business, it was American techniques and marketing know-how which unfortunately made cigarettes a worldwide success. The Americans used flue-cured tobacco and new technologies of mass production, and they introduced safety matches and started a ruthless advertising and marketing campaign. Compared to the traditional dark air and fire-cured varieties of tobacco, flue-cured tobacco produces much milder smoke, which is easier to inhale than the alkaline smoke of air and fire-cured tobacco. Mass production lowered the price, and the introduction of the safety match reduced the risk of fire and facilitated smoking in public. It was James B. Duke who in 1877 launched an international advertising and marketing campaign which got the practice of cigarette smoking off the ground.

It is impossible here to go into detail about the advertising and marketing strategies used by the tobacco industry, but the psychologically astute and perfidious approach can be illustrated by two examples: First, how was the market opened to women? After the First World War, the advertisement for Chesterfield showed a couple in a romantic setting: the man smoking and the woman in a sensuous pose. The caption was: “Blow some my way”. In 1927, Philipp Morris advertised its brand Marlboro, initially intended for women (in contrast to the image of Marlboro as the cigarette for the tough Marlboro rider in postwar years). The advertisement showed a woman holding a cigarette, with the caption: “Women when they smoke at all quickly develop discriminating taste”. The hard-hitting message that smoking prevented weight gain was launched with the caption: “Reach for a Lucky instead of a sweet”. And this was backed up by numerous testimonials of physicians on the desirable effects of cigarettes on body weight and figure. The message was reinforced by headlines such us “pretty curves win”. Small wonder that the cigarette was adopted by women as a symbol of emancipation.

The versatility of the money-powered marketing industry is illustrated by its reaction to a crisis in 1954 when a publication under the auspices of the American Cancer Society documented the causal relationship between cigarette smoking and lung cancer. The tobacco industry quickly found solutions. First, a research committee was established intended to undermine the evidence that smoking was related to cancer. More importantly, to lull the consumer into a sense of safety, filter-tipped cigarettes were introduced to satisfy his desire for a “safer” cigarette. Filter-tipped cigarettes allegedly filtered out and removed carcinogenic substances from smoke. To the disgrace of the medical profession, such cigarettes were even recommended by physicians (Fig. 2). The introduction of the filter-tipped cigarette was certainly sweetened for the tobacco industry by a large economic benefit, since less tobacco went into filter-tipped than regular cigarettes.

Fig. 2. Cigarette advertisement with physician’s advice. We thank P.T. Sawicki (Düsseldorf, Germany) for making us aware of this advertisement.

SMOKING AND DIABETIC NEPHROPATHY

An initial communication by Christiansen, suggesting that smoking is an independent risk factor for diabetic nephropathy [1], was confirmed by two Scandinavian authors [22, 23], but these efforts failed to attract wider attention. In the early 1980s, a number of studies examined the influence of blood pressure and glycaemic control on the development of diabetic
nephropathy and retinopathy respectively, but, as pointed out by Mühlhauser et al. [2, 24], smoking was not even considered as a potential confounder.

Meanwhile, the evidence became overwhelming. In a cross-sectional case-controlled study in a large cohort of 1,254 diabetic patients, cigarette-smoking patients were pair-matched with non-smoking patients. The proportion of patients with proteinuria was significantly higher among smokers, while HbA1c levels or hypertension control were comparable in both groups [24]. These findings have been confirmed [25] and recently extended by the results of prospective studies. Chase et al. [26] found more marked progression of albuminuria in smokers and noted that albuminuria decreased significantly when subjects stopped smoking. The odds ratio for developing a significant increase of albuminuria was 2.2 for smokers. In a prospective study, Sawicki et al. [27] examined 93 patients with Type 1 diabetes of long duration and diabetic nephropathy. They were well-controlled with respect to glycaemia and blood pressure. Progression occurred in 53% of smokers compared to 11% of non-smokers and 33% of ex-smokers.

In general, smoking adversely affects four different aspects of nephropathy [3]: (i) it increases the risk of development of albuminuria [26]; (ii) it shortens the time interval between onset of diabetes and onset of albuminuria or proteinuria; (iii) it accelerates the rate of progression from the stage of microalbuminuria to persistent proteinuria (i.e. overt diabetic nephropathy) [22, 24]; and (iv) it accelerates the rate of progression of diabetic nephropathy to end-stage renal disease [25, 28]. In the study of Biesenbach et al. [28], the rate of loss of the glomerular filtration rate (GFR) was 1.44-fold higher in smoking than in non-smoking patients with Type 1 diabetes.

An association between smoking and nephropathy has also been found in Type 2 diabetes, although the situation is somewhat more complex [3]. Smokers have a greater risk of developing Type 2 diabetes [29, 30]. In these two studies, the relative risk of developing Type 2 diabetes was respectively 1.94-fold and 1.5-fold higher than for non-smokers.

In cross-sectional studies of patients with newly diagnosed Type 2 diabetes, smoking was associated with a higher urine albumin/creatinine ratio [31] and a higher frequency of albuminuria [32]. While some cross-sectional analyses failed to confirm an association between smoking and nephropathy [33], a prospective study showed that smokers had a 2.5-fold higher risk of developing gross proteinuria [34]. This finding is in line with that of another prospective study in which smoking was an independent predictor for de novo development of microalbuminuria in Type 2 diabetic patients [35]. In a large population-based cross-sectional study of patients with established Type 2 diabetes, cigarette smoking also emerged as an independent variable related to microalbuminuria [36]. Furthermore, in Type 2 as in Type 1 diabetes, smokers progressed more rapidly from microalbuminuria to gross proteinuria and lost GFR at a faster rate [28].

## SMOKING AND NON-DIABETIC RENAL DISEASE

Until recently, very little was known about the effects of smoking on renal prognosis in patients with non-diabetic renal disease. Chapman et al. [6] found that patients with autosomal dominant polycystic kidney disease (ADPKD) and established proteinuria had a higher pack year smoking history than non-proteinuric patients. Furthermore, in a retrospective study on 160 patients with lupus nephritis, smoking at the time of onset of nephritis emerged as an independent risk factor for more rapid development of terminal renal failure [5], independent of hypertension and immunosuppressive treatment.

A retrospective multicentric case-control study including 582 patients from 9 centres in Germany, Italy and Austria investigated patients with IgA glomerulonephritis (as a model of inflammatory renal disease) and ADPKD (as a model of non-inflammatory renal disease) [7]. The cases were patients who had progressed to end-stage renal failure, and the controls were patients who were not in end-stage renal failure and whose serum creatinine had failed to progress to values above 3 mg/dl. In male patients, the crude odds ratio showed a significant dose-dependent increase of the risk of progressing to end-stage renal failure (Table I). The number of female patients was insufficient for appropriate statistical analysis. Interestingly, in multivariate analysis tobacco-associated risk was clearly evident in patients who had not been treated with angiotensin-converting enzyme (ACE) inhibitors, but no longer demonstrable in smokers on ACE inhibitor treatment (Table II). These findings clearly indicate that smoking confers a substantial renal risk and illustrate that this is not unique to diabetic nephropathy. It is also true for glomerular and non-glomerular renal disease of inflammatory or non-inflammatory origin.

## ACUTE EFFECTS OF SMOKING ON RENAL HAEMODYNAMICS

Our group attempted to define the acute effects on renal haemodynamics of smoking as compared to sham smoking in a study on volunteers, i.e. occasional smokers who had abstained from smoking as documented by urinary cotinine measurements [8]. Systemic haemodynamics, hormonal changes and renal haemodynamics were compared between a sham smoking and a smoking period. As shown in Table III, smoking caused a highly significant acute increase in
### Table I. Crude smoking-associated risk of end-stage renal failure in male patients with IgA-glomerulonephritis or autosomal dominant polycystic kidney disease [7].

<table>
<thead>
<tr>
<th>Pack-years</th>
<th>Cases [N, (%)]</th>
<th>Controls [N, (%)]</th>
<th>Odds ratio</th>
<th>95 %-confidence interval</th>
<th>P value[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>26 (36)</td>
<td>47 (65)</td>
<td>1.0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5-15</td>
<td>17 (24)</td>
<td>11 (15)</td>
<td>3.5</td>
<td>1.3-9.6</td>
<td>0.017</td>
</tr>
<tr>
<td>&gt;15</td>
<td>29 (40)</td>
<td>14 (19)</td>
<td>5.8</td>
<td>2.0-17</td>
<td>0.001</td>
</tr>
</tbody>
</table>

[1](Wald $\chi^2$).

### Table II. Smoking-associated risk of end-stage renal failure (stratified for ACE-inhibitor treatment and adjusted for systolic blood pressure) in male patients with IgA-glomerulonephritis or autosomal dominant polycystic kidney disease [7].

<table>
<thead>
<tr>
<th>Pack-years</th>
<th>ACE-inhibitor</th>
<th>No ACE-inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95 %-confidence interval</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>1.4</td>
<td>0.3-7.1</td>
</tr>
</tbody>
</table>

[1](Wald $\chi^2$)

### Table III. Effect of smoking vs. sham smoking on systemic circulation in 15 healthy volunteers [8].

<table>
<thead>
<tr>
<th>Period</th>
<th>Sham smoking</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minutes</td>
<td>MAP (mmHg)</td>
</tr>
<tr>
<td>Basal</td>
<td>30</td>
<td>93.2 ± 10.9</td>
</tr>
<tr>
<td>Cigarette</td>
<td>10</td>
<td>95.6 ± 10.6a</td>
</tr>
<tr>
<td>Pause</td>
<td>6</td>
<td>94.9 ± 12.9</td>
</tr>
<tr>
<td>Cigarette</td>
<td>10</td>
<td>95.1 ± 10.7</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure. HR = heart rate. a $P<0.05$, intraindividual differences, basal vs. sham smoking, by paired t test. b $P<0.001$, intraindividual differences, basal vs. smoking, by paired t test. c $P<0.001$, intraindividual differences, basal vs. smoking, by paired t test.

### Table IV. Hormonal changes during smoking in 15 healthy volunteers [8].

<table>
<thead>
<tr>
<th>Period</th>
<th>Norepinephrine (pg/mL)</th>
<th>Epinephrine (pg/mL)</th>
<th>Arginine vasopressin (pg/mL)</th>
<th>Active renin (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sham smoking</td>
<td>smoking</td>
<td>sham smoking</td>
<td>smoking</td>
</tr>
<tr>
<td>basal</td>
<td>325 ± 129</td>
<td>293 ± 124</td>
<td>37.0 ± 13.0</td>
<td>2.05 ± 1.04</td>
</tr>
<tr>
<td>cigarette</td>
<td>332 ± 127</td>
<td>348 ± 128</td>
<td>27.0 ± 11.0</td>
<td>1.44 ± 0.60</td>
</tr>
</tbody>
</table>

a $P<0.01$, intraindividual differences, basal vs. smoking, by paired t test. b $P<0.001$ by Wilcoxon test for paired differences. c Median, 4.00 pg/mL; range 0.90-83.9 pg/mL.
mean arterial pressure (MAP) and heart rate. This was accompanied by an increase in epinephrine, norepinephrine and arginine vasopressin concentrations. In contrast, presumably as a response to the increase in MAP, active plasma renin decreased (Table IV). In these healthy volunteers, smoking, as compared to sham smoking, caused a significant decrease in GFR and filtration fraction (FF) as measured by radioisotope infusion clearance (Table V). FF, a surrogate marker of glomerular capillary pressure, decreased in healthy volunteers, which is difficult to reconcile with the notion that smoking aggravates renal risk since it is assumed that progression is mediated by an increase of glomerular capillary pressure. To take this issue one step further, the renal effects of smoking were compared in patients with IgA-glomerulonephritis (IgA-GN) and in healthy volunteers (Table V). While the increase in MAP and heart rate was similar in patients with IgA-GN and volunteers, a significant decrease in GFR and FF was not apparent in patients with IgA-GN. It was speculated that smoking-induced vasoconstriction of afferent (i.e. preglomerular) vessels is less pronounced in patients with glomerular disease in whom preglomerular vessels are known to be dilated. Persistence of vasodilation in the face of an increase in blood pressure would permit transmission of a larger proportion of systemic blood pressure into the glomerular microvasculature. In line with this hypothesis, a significant increase in the urinary albumin/creatinine ratio was observed during smoking in pa-

### Table V. Contrasting effects of smoking on renal haemodynamics in volunteers and patients with IgA-glomerulonephritis [8].

<table>
<thead>
<tr>
<th></th>
<th>Volunteers (n = 15)</th>
<th>IgA-GN (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GFR (mL/min per 1.73 m²)</td>
<td>FF (%)</td>
</tr>
<tr>
<td>- basal</td>
<td>120 ± 17.7</td>
<td>21.3 ± 4.24</td>
</tr>
<tr>
<td>- smoking</td>
<td>102 ± 19.3b</td>
<td>17.4 ± 3.41b</td>
</tr>
<tr>
<td>IgA-GN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- basal</td>
<td>109 ± 18.3</td>
<td>19.8 ± 4.14</td>
</tr>
<tr>
<td>- smoking</td>
<td>111 ± 34.0</td>
<td>18.9 ± 6.32</td>
</tr>
</tbody>
</table>

*P < 0.005, intraindividual differences, basal vs. smoking, by paired t test. b P < 0.001, intraindividual differences, basal vs. smoking, by paired t test. c P < 0.006, intraindividual differences, basal vs. smoking, by paired t test. d P < 0.0001, intraindividual differences, basal vs. smoking, by paired t test. GFR = glomerular filtration rate. FF = filtration fraction. RVR = renal vascular resistance. MAP = mean arterial pressure.
Smoking 
\[\text{sytamathic activation}\] 
\[\text{increased circulating epinephrine}\] 
\[\beta_1\text{-adrenergic stimulation, e.g. of juxtaglomerular apparatus}\] 
\[\text{renin}\] 
\[\text{angiotensin II}\]

Fig. 4. Hypothetical sequence of mechanisms underlying the renal effects of smoking.

- Smoking interferes with IgA-GN. This hypothesis would also explain the finding of Ekberg et al. [37] that GFR is higher in patients with Type 1 diabetes who smoke.

- The studies of Cryer et al. [38] clearly documented activation of the sympathetic nervous system during smoking. This finding has recently been extended by Grassi et al. [39] and Hausberg et al. [40], who found that smoking caused an increase in heart rate and circulating norepinephrine and epinephrine, whereas sympathetic activity in the sural nerve decreased, presumably as a baroreceptor-mediated response to acute increase in blood pressure. A study of the effect of pretreatment with the \(\alpha\)-adrenergic blocker prazosin (compared to placebo) and with atenolol (compared to placebo) showed that the former failed to affect the change in renal haemodynamics, while the latter abolished renal haemodynamic changes after smoking [41]. The changes in GFR after placebo pretreatment, as compared to atenolol pretreatment, are shown in Figure 3. This observation suggests that \(\beta_1\)-adrenergic stimulation, presumably of the juxtaglomerular apparatus, is involved. In view of the protective effect of ACE inhibitors against deterioration of renal function in smokers (Table II), it is cautiously speculated that \(\beta_1\)-adrenergic stimulation of the juxtaglomerular apparatus leads to a local increase of angiotensin II within the kidney (Fig. 4).

**CHRONIC EFFECTS OF SMOKING ON RENAL FUNCTION IN SUBJECTS WITHOUT RENAL DISEASE**

Smoking is known to cause intimal hyperplasia and wall-thickening of arteries and arterioles in various organs [42], including the kidney [43-45]. The signal causing such vascular damage is unknown. It has been postulated [46] that stimulation of \(\alpha\)-adreno-receptors by nicotine, effects of smoke components (e.g. CO-mediated hypoxia), generation of reactive oxygen species, and impaired endothelial cell function (as reflected by impaired endothelin-dependent vasodilation) play a role. In line with this idea, the absence of the initial vasodilatory response to low concentrations of endothelin 1 in smokers is thought to be mediated via release of prostacyclin and nitric oxide [47].

Apart from such structural changes, there is also clear evidence for impaired renal haemodynamics [48, 49] and impaired glomerular permeability [50-52] in chronic smokers. The extent to which these defects are triggered by, or interact with, the above-mentioned acute renal effects [8] remains to be established. The acute renal effects can be reproduced by nicotine-containing chewing gum [8], while the chronic effects of smoking are presumably more complex, as detailed below.

Gambaro et al. [48] compared 24 age- and sex-matched non-smokers with 30 smokers with no known vascular disease or further risk factors. Cigarette smokers had a significant reduction of effective renal plasma flow (ERPF), whereas GFR remained normal. Concomitantly, slightly higher plasma endothelin concentrations were found, possibly reflecting endothelial cell dysfunction. The discrepancy between reduced plasma flow and unchanged GFR is puzzling. It has been speculated that there is an adaptive increase in glomerular perfusion rate and pressure, as seen in hypertensive nephroangiosclerosis and cyclosporin A nephrotoxicity [9]. Halimi et al. [49] examined the acute effect of smoking on renal haemodynamics in non-smokers and chronic smokers. In non-smokers, smoking reduced GFR and renal plasma flow (RPF), as in the study of Ritz et al. [8]. However, no acute renal haemodynamic changes were seen in chronic smokers. Similarly, urinary excretion of cyclic guanosine monophosphate (cGMP), a mediator of the effects of nitric oxide increased in chronic smokers, but decreased in non-smokers [49]. The authors speculated that increased compensatory nitric oxide release helps overcome smoking-induced renal vasoconstriction.

Further evidence for an adverse effect of smoking on renal function comes from investigations of albumin and protein excretion in hypertensive and normotensive individuals. Hörner et al. [51] examined 631 normotensive and hypertensive elderly individuals and measured urinary albumin concentration in the morning urine. By multivariate analysis, smoking emerged as the single most potent predictor of albuminuria. Similarly, a correlation between smoking and albumin excretion was noted in the study of Mimran et al. [50].

**POTENTIAL MEDIATORS OF SMOKING-INDUCED CHRONIC RENAL DAMAGE**

Smoking interferes with a number of systems which are potentially capable of inducing renal dam-
These include alterations in endothelial cell structure [53] and function, particularly release of nitric oxide [45, 46, 54], diminished prostacyclin, increased thromboxane release, release of isoprostanes (which are synthesised independently of cyclooxygenase by the interaction of arachidonic acid with reactive oxygen species [55]), inhalation of and generation of advanced glycation end-products, increased platelet aggregation [56], adhesion of monocytes to endothelial cells [57, 58], expression of adhesion molecules (ICAM-1, ELAM-1) by endothelial cells, endothelial apoptosis, and endothelial cell desquamation [53].

The potential importance of smoke ingredients other than nicotine is well illustrated by observations in the Framingham study that non-smoking modalities (e.g. snuffing or chewing), as compared to smoking, failed to affect cardiovascular risk and insulin resistance adversely [59]. It is therefore imperative to define the mediators of smoke-induced damage exactly and to characterise the steps by which tissue damage, including renal injury, is effected.

### Table VI. Potential pathomechanisms of smoking-induced renal injury [60].

<table>
<thead>
<tr>
<th>Pathomechanism</th>
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<tbody>
<tr>
<td>• Increase in blood pressure and heart rate</td>
</tr>
<tr>
<td>• Alteration of diurnal blood pressure rhythm</td>
</tr>
<tr>
<td>• Increased sympathetic nerve activity</td>
</tr>
<tr>
<td>• Increase in renal vascular resistance leading to decrease in GFR and RPF (ET-1 mediated?)</td>
</tr>
<tr>
<td>• Arteriosclerosis of the renal arteries and the intrarenal arteries and arterioles (ET-1?)</td>
</tr>
<tr>
<td>• ET-1-mediated proliferation and matrix accumulation of VSMC, endothelial cells and mesangial cells</td>
</tr>
<tr>
<td>• Tubulotoxicity</td>
</tr>
<tr>
<td>• Direct toxic effects on endothelial cells</td>
</tr>
<tr>
<td>• Alteration of the prostaglandin/thromboxane metabolism</td>
</tr>
<tr>
<td>• Oxidative stress through generation of reactive oxygen species</td>
</tr>
<tr>
<td>• Nitric oxide depletion</td>
</tr>
<tr>
<td>• Impairment of endothelial cell-dependent vascular dilation</td>
</tr>
<tr>
<td>• Increased adhesion of monocytes to the endothelium</td>
</tr>
<tr>
<td>• Carbon monoxide-induced hypoxia</td>
</tr>
<tr>
<td>• Increased clotting of platelets</td>
</tr>
<tr>
<td>• Impaired lipoprotein and glycosaminoglycan metabolism</td>
</tr>
<tr>
<td>• Modulation of immune response</td>
</tr>
<tr>
<td>• Antidiuresis (vasopressin)</td>
</tr>
<tr>
<td>• Increased insulin resistance</td>
</tr>
</tbody>
</table>

ET-1 = endothelin-1. GFR = glomerular filtration rate. RPF = renal plasma flow. VSMC = vascular smooth muscle cells.

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