Radboud Repository



PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link. http://hdl.handle.net/2066/27691

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

The changing appreciation of tobacco products in human society

by H.F. Linskens

Department of Ecology, University of Nijmegen, NL 6525 ED Nijmegen, The Netherlands

Communicated at the meeting of September 29, 1997

ABSTRACT

Tobacco products are mainly consumed in three different forms: as smoke, by burning tobacco leaves (pipe, cigar, cigarette); as powdered dry leaves, called snuff; by masticating and gnawing, called chewing quid. During the centuries the usage of tobacco has passed many stages; firstly used as a ritual herb and for the preservation of dead bodies; later as a medicine for numerous diseases; furthermore a pleasant semi-luxury; an agreeable status symbol; a tranquilizer and a suggestive stimulator; a cancer promoter, ending up as a political and socio-economic issue and finally condemned as an addictive drug. Besides anti-smoke compaigns the recent ventures have resulted in the development of smokeless tobacco, weakened and safe cigarettes. The decline of appreciation of tobacco products in the Western World is contrasted by the rise of tobacco as an experimental plant, and as a possible candidate for the production of edible protein.

1. INTRODUCTION

During the last 40 years, tobacco has been one of the most controversial of cultivated plants. There are about 64 species within the genus *Nicotiana*, two of which, the red or rose-flowered *Nicotiana tabacum* L. and the yellow-flowered *Nicotiana rustica* L., i.c. smoke tobacco and farmer's tobacco respectively, conquered the world (Koenig, 1938b; Bergmark, 1958) and are known to the majority of the inhabitants of the earth. Nicotine is the most abundant alkaloid and may provide a pleasurable alerting effect associated with tobacco use (Andersen, 1994).

Cultivated tobacco is an allotetraploid perennial that arose by natural hybridization of *Nicotiana sylvestris* Spegaz and Comes, with *N. tomentosiformis* Goodsp. Although the genus is considered to be of tropical origin, the two species are cultivated worldwide in areas with frost-free periods sufficiently long to permit the crop, that is the leaves, to mature. Thus, tobacco culture is found between 60° N and 40° S. A couple of horticultural species are widely grown as ornamentals but are not used as drug plants.

Both cultivated species originated in South America. Seeds were first brought from America to Portugal in 1519 and to other parts of Europe in the middle of the 16th century by Francisco Hernandez (1514–1587), physician to Philips II, and by the French monk and later Calvinist André Thevet (1502–1590). While tobacco has been known by many names, the genus *Nicotiana*, was named after Jean Nicot de Villeman (1530–1600), the French ambassador to Portugal, by Linnaeus. When Nicot was called back to Paris in 1560 he introduced the fashion of taking tobacco in the form of snuff at the royal court.

The main alkaloid, nicotine, was first isolated by two German students, Wilhelm Heinrich Posselt (1806–1877) and Karl Ludwig Reimann (1804–1872). They called it nicotine in their thesis delivered to the University of Heidelberg in 1828. The correct chemical structure was determined by Pinner in 1893 and confirmed by synthesis by Picet in 1923 (Schadewaldt, 1967). The alkaloid concentration in tobacco leaves ranges between 0.2 and 8.0%, and is influenced by genetics, agricultural practice, climatic and soil conditions, stalk position and time of harvesting, plant diseases and curing procedure. Nicotine is the most abundant alkaloid and considered to provide a pleasurable, alerting effect associated with tobacco use (Andersen, 1994).

Alkaloid synthesis in tobacco plants takes place in the root system (Mothes and Hieke, 1943; Hegnauer, 1973). Synthesis is controlled genetically by two major genes, modified by quantitative factors or minor genes, which can be influenced greatly by the environment. After formation in the root, the nicotine is transferred into the leaves and stems where it accumulates. Total alkaloid levels are highest in the upper levels of the plant at low temperature, a fact which has consequences for the harvesting procedure in the various regions of production, and influences the quality of the raw material for tobacco preparation. However, tobacco is not utilized as fresh leaves, but in a transformed form. Outstanding effects of ageing the leaves (so inducing a slow and mild fermentation) or enforced fermentation, accompanied by a vigorous chemical change, are: the development of the desired aroma, elimination of harshness, improvement of the bitter taste, and disappearance of green shades. The tobacco leaf as a raw product acquires by fermentation processes the darkened brown colour characteristic of tobacco products, diminished luster and stickiness, improved combustibility, and reduction of irritating qualities of smoke (Andersen, 1994).

Tobacco products are mainly consumed in three different forms: as smoke,

by burning tobacco leaves in the cut form of pipe tobacco, as cigars of rolled leaves, packed in a paper wrapper or tube as cigarettes, or by fumigation; as powdered, dry leaves or snuff applied to the mucous membranes of the nose; and by masticating and gnawing dried and perfumed ribs, stalks and stems, between the teeth and the cheek pocket of the mouth, called chewing quid. In Sweden the tobacco bag for the cheek is called 'snus'.

Over the centuries tobacco has had a variety of different uses: first as a ritual herb and for the preservation of corpses; later as a medicine for numerous chest pains and other complaints; as a pleasant semi-luxury; an agreeable status symbol; a praised tranquilizer or as a suggestive stimulator; it was condemned as an allergen and a carcinogen, but was recognized for some years as an insecticide and a popular cure for aphids, finally ending as a political issue and being classified as a habit forming and later an addictive drug.

3. TOBACCO AND CIVILIZATION

Tobacco plays a role in nearly all the numerous novels of the English writer William Somerset Maugham (1874–1965). This is most impressive in the story of 'The Verger', about a sacristan and non-smoker in a very classy congregation. When a new vicar came in, it became evident that the verger could neither write nor read. After 16 years of service he was dismissed on the spot by the young vicar and the two venerable church-wardens of St. Peter's. The discharged verger locked the church door behind him and took the wrong street, his heart was heavy, he did not know what to do with himself. The verger was a total abstainer, but suddenly, being disappointed and tired, he wanted a cigarette. He looked for a shop, where he could buy a packet of Gold Flake, but in the long street there was not a single shop where he could buy a cigarette. And he decided that he would set up in business as a tobacconist, and he did very well.

After a year he took a second shop and put in a manager. This was also a success. In the course of ten years he acquired no less than ten shops and he was making money hand over fist. He went to the bank every Monday morning and one day the cashier told him, that he had a little over 30,000 pounds. He suggested that instead of a savings account, a better investment would be made in stocks and shares. The bank clerk needed only his signature to authorize the job. But the former verger now had to confess that he could not read and write. The bank manager was very surprised that this man had been able to build up this important bussiness in tobacco products and had amassed a fortune of 30,000 pounds, without being able to read or write. 'Good God, man, what would you be now, if you had been able to write and read!' The former verger answered: 'I can tell you that, Sir' a little smile on his still aristocratic features 'I'd be a verger of St. Peter's Neville Square'.

This story of Somerset Maugham puts in a nutshell the problems of the appreciation of tobacco.

It seems interesting to me to note the changing appreciation of tobacco

products in human society by the reflection of literature, art, drama and movies, in television and on the stage, in the performing arts, and so on. But I am not an expert in these fields, so I shall restrict myself to numbers and facts and statistics.

4. HISTORY OF TOBACCO CONSUMPTION

The history of tobacco starts with the invention of smoking by the Mayas in Mexico and South America respectively, about one and a half thousand years ago (Seibert, 1980a,b); they had discovered the relaxing effect of smoked tobacco. The American Indians respected the tobacco pipe as a sign of peace, like the Europeans the white flag of a negotiator. The Indians smoked principally as a religious rite, as an offering or respect to a superior, or to cure a disease. Australia has about 20 species of *Nicotiana* (Keller, 1979), some of which were chewed and traded by the Aborigines (Peterson, 1979). Smoking, however, was not introduced until the advent of American tobacco via Europe (Horton, 1981). There are many references to Indian use of tobacco in South America (Wilbert, 1987), but it was the European who made a purely pleasurable indulgence of the practice (Saunders, 1978).

The history of tobacco in Europe started with the discovery of America by Christopher Columbus in 1492 (Koenig, 1938a; Schadewaldt, 1967; Herks, 1976; Seibert, 1980a,b) (fig. 1).

Before going into the history of the use of tobacco by the European at the beginning of the 16th century we should note the recent discovery that nicotine, the main alkaloid in tobacco, was already known in ancient Egypt. Recently (Balabanova et al., 1992, 1993) the presence of nicotine in hair, soft tissue and bone samples has been demonstrated from Egyptian mummies. These findings indicate the use of nicotine during life. Smoking was unknown in ancient Egypt, however fumigation was widespread in religious rituals and folk medicine. Consequently, it was possible that nicotine was inhaled during fumigation with Nicotiana plants, but also with other plants containing that alkaloid as a secondary alkaloid. These investigations indicate that tobacco plants, or plants which contain nicotine, were used in ancient Egypt long before the time of Columbus. In addition, in the mummy of Ramses II (Alfieri, 1931; Steffan, 1985) the remains of tobacco beetles have been found in the abdomen and cervical region of the mummy by electron microscopy and the remains of Nicotiana leaves (Layer-Lescot, 1985). These leaves had apparently been used in the process of embalming.

If we ignore unreliable reports from China that pipes were in use 500 years before Christ and in Melanesia and Africa tobacco may have been smoked incidentally, the first report on tobacco smoking comes to Europe through the discovery of America (Stahl, 1938). In the history of Columbus by his natural son, Fernando (Colombo, 1571) reference is made to tobacco, from his father's unpublished journal. Fernando stated that the natives where his father first landed, offered dried leaves of tobacco as a gift, and that two sailors who ex-

plored the interior of the island (Cuba) earlier called Ferandina, on November 2nd, 1492, were the first white men to see the cigar in use. Other histories report that soon after the first landing on the island of Guanahani, which Columbus later called San Salvador, on October 15, 1492, the Indians offered the Europeans dried leaves, although the visitors did not understand their value or meaning (Stepney, 1981). Also during the second trip to America the monk Romano Pana reported in March 1496 the Indian habit of smoking tobacco in the form of enrolled leaves, cigars, and in pipes (Koenig, 1938a,b; Schadewaldt, 1967).

The social significance of the pipe among the Canadian Indians and the religious esteem in which they held tobacco was recorded at the beginning of the 17th century (Lescarbot, 1609). It is no wonder that scientific botany also became interested in this strange plant. The earliest publication in England, which fully described and illustrated tobacco, was in 1570 (L'Obel and Pena, 1570/71). Reference to a crude cigar smoked by returned mariners, reported that the habit 'induced a pleasing drunkness and cleared the head of moisture humours'. The Italian herbalist P.A. Mattioli (1586) was one of the first to advise caution in the medical employment of the 'violent herb', tobacco.

The modern scientific terminology for the two chief species of tobacco, Nicotiana tabacum and N. rustica, were first introduced in Linnaeus' 'Species Plantarum' in 1753 (Linné, 1753).

During the 16th century tobacco cultivation became widespread in Europe, and medical use was recommended (Magnen, 1658). Various indications were reported, e.g. treatment of ulcer, headache, asthma, vermin, chiggers, intestinal worms (Grimé, 1979). As well as an ointment and as a sternutory to cause sneezing, tobacco was also recommended as a powder, watery extract and as an enema (infusion into the anus).

Even in aristocratic society, the taking of snuff replaced smoking for quite some time. Snuff boxes were 'objects de fashionables' (Gottsegen, 1940) in several periods. Tobacco was considered for quite some time as a general antidote. Taking snuff was suggested for general health promoting effects, so that 'the brain was enforced to release liquid'.

The strangest application was the use of tobacco smoke to revive people in suspended animation. Special instruments were constructed to apply tobacco smoke via the anus (Schadewaldt, 1967). In time of plague tobacco smoke was recommended for disinfection, later as a mixture together with sulphur for decontamination of ships.

Opposition against tobacco for semi-luxurious use came not only from the churches, e.g. by Pope Urban VIII (1568–1644), but also from the government. For example, King James of England (1566–1625) himself wrote a paper entitled 'A counterblast to tobacco' and called himself a 'Micocapnus' that is, a hater of smoke.

One of the few remaining achievements of the bourgeoise revolution of 1848 was the right to smoke in public places, on streets and public grounds, which had been prohibited by police decree since 1661 in Berlin. But proscriptions

and fines could not prevent the worldwide introduction of tobacco products (Böse, 1965; Kneist, 1981; Knobloch, 1991). Tobacco consumption became acceptable at court.

After the isolation of nicotine and the first pharmacological experiments, the application of tobacco as a medicament ended. But in the meantime tobacco uses had changed. The 19th century was the age of cigar and tobacco quid, whereas in the 20th century the cigarette conquered the world.

An essential step was the invention of the cigarette-making machine by Bensack (1875), patented in the USA in 1881, which became one of the heralds of the era of mass production (Ashton and Stepney, 1983). During and after the World War I the spread of cigarette smoking was not to be contained. The low cost and easy convenience of the cigarette compared with the cigar, the growth of leisure time and the democratization of society, provided conditions conductive for mass consumption of tobacco. The invention of the safety match contributed greatly to the ritual of cigarette smoking. Introduction of mellower tobacco encouraged inhalation of smoke. After the war in the post-1918 period one also observed the rise of the female smoker in public.

The introduction of the filter cigarette, first in 1929 by du Maurier in Britain, counteracted the first epidemiological studies, which showed that non-smokers live longer than smokers. The evidence of the link between cigarette smoking and lung cancer by Doll and Will (1950/1956) stopped the increase of the smoking habit in European and American societies (Albrecht, 1988).

Cigarette sales in Europe and North America began to level off in the middle of the 80's as word spread of smoking's health toll. The world cigarette industry, however, is hardly in despair, for a vast potential market in the Third World is presently being developed intensively (Eckholm, 1978). There is doubt that tobacco will disappear as it is a habit-forming drug (Baker, 1975).

5. WHY DO PEOPLE SMOKE?

There is a huge body of literature on this question, but the question is still asked, and to a great extent is still unanswered (Robinson and Pritchard, 1992a).

The traditional belief is that smoking and originality and cleverness in literature production are inseparable. Many artists have conditioned their intellectual and creative efforts upon the physical act of smoking (Hamilton, 1928). If one compares a list of smokers and non-smokers (table I) it is evident that no scientific conclusion can be made on the effect of tobacco on the efficiency in thought or action, either in a positive or negative direction.

One can distinguish between the pharmacological aspect and the non-pharmacological aspects of tobacco consumption. The pharmalogical effect produced by tobacco consumption is attributed to the main alkaloid, nicotine. The nicotine is absorbed by the smoker from the inhaled mainstream smoke.

Table I. List of some smokers and non-smokers (Hamilton, 1928; Warburton, pers. comm.)

Smokers	Non-smokers	~
Samuel Becket	Idi Amin Dada	
Pope Benedict XIII	Fay Bakker	
Niels Bohr	Jim Bakker	
Charlie Chaplin	Honoré de Balzac	
Agatha Christie	John Burroughs	
Winston Churchill	Robert Burton	
Charles Darwin	William Cowper	
Charles Dickens	William Cullen Cryant	
Albert Einstein	Johan W. Goethe	
Thomas S. Eliot	Heinrich Heine	
Frederico Fellini	Adolf Hitler	
Henry Ford	Victor Hugo	
Ernest Hemmingway	Saddam Hussein	
Rudyard Kipling	Pope Innoscenz X	
Stan Laurel and Oliver Hardy	King James I	
Carl von Linné	David Koresh	
Thomas Mann	Robert Edward Lee	
Golda Meir	Abraham Lincoln	
Robert Oppenheimer	Thomas Macaulay	
Wolfgang Pauli	John Henry Newman	
Pablo Picasso	Richard Nixon	
Edgar Allan Poe	Jean J. Rousseau	
Franklin Delano Roosevelt	John Ruskin	
Bertrand Russell	Russel Sage	
Ernest Rutherford	Percy Bysshe Shelley	
Jean Paul Sartre	Robert Southey	
John Steinbeck	Jonathan Swift	
James Watson	Algernon C. Swinburne	
Evelyn Waugh	Pope Urban VIII	
Orson Wells	Voltaire	
Virginia Wolf	John G. Whittier	

5.1. Pharmacological effects

The pharmalogical effects fall into two main categories:

- the peripheral effect of nicotine is mainly stimulatory and increases the heart beat. Smokers report that this is most noticeable with the first cigarette of the day (Benowith, 1978), and also that there is an increased mental alertness.
- the calming effect, which helps the smoker to function in stressful situations of daily life. More that 80% of the 2000 smokers questioned report the pleasurable relaxation effect as the most important motive for smoking.

These two seemingly contradictory motivations, mental stimulation on one side, and mental relaxation on the other side, form the so-called 'nicotine paradoxon' (Gilbert, 1979).

The biological potency of nicotine has apparently contradictory effects: it may reduce arousal, anxiety and lethargy – no wonder that in all armies of the

world in preparation for battle attacks, tobacco and alcohol are distributed to the troops. And on the other side is the strength of nicotine as an unconditioned stimulus: its delivery to the central nervous system is rapid, about 7 seconds from the moment of inhalation (Pomerleau and Pomerleau, 1987; Fisher et al., 1993). Mental relaxation and mental stimulation combined are the mysterious attraction of tobacco.

5.2. Non-pharmacological effects

The non-pharmacological aspects of tobacco smoking may be even more important. They comprise: the taste of the tobacco smoke; this explains the great variety of tastes of various tobacco brands on the market. They include also the sensory response in the throat and the upper airways of the smoker, a finding which is supported by experiments with anesthetization of the mouth, throat and upper airways resulting in a significantly reduced desire to smoke (Rose et al., 1984). The social aspect of smoking cannot be underestimated. The ceremony of taking out a container with tobacco or tobacco products (e.g. the snuff box), the lifting of a cigarette or cigar, checking the smell, the personal preparation of the piece by squeezing or pushing, cutting the cigar tip, extracting the straw halm (from certain type of cigars), lighting the match or the presentation of the precious lighter – all these steps of a ceremony precede the social event of smoking. All contributed to the rapid spread of tobacco consumption (Breslow and Johnson, 1993). The social aspects of smoking are at present the main stay of the advertising industry, linking smoking with adventure, success in life and love, pleasant social contacts.

The turning point of tobacco consumption in the Western World is lined with two publications by the U.S. Surgeon-General (SGR) of the Public Health Serive (U.S. Department of Health, 1964, 1988), followed by the Californian Proposition 99 (West-Consort, 1990) on tobacco and its impact (Breslow and Johnson, 1993).

Recognition of the devastation of health from tobacco use began in the 1930's, when the biostatistician Raymond Pearl (1933) demonstrated in a two page article in Science that 'smoking is statistically associated with an impairment of life duration'.

Since then it has been recognized that tobacco consumption is the largest single preventable cause of mortality, responsible for the shortening of about 400,000 lives each year, that is about one sixth of all deaths in the U.S. (Breslow and Johnson, 1993), or 1200 per day. Diseases caused by excessive tobacco consumption are: coronary heart disease, lung cancer, chronic lung disease, and stroke.

The general question about the attraction of tobacco consumption can be more specialized by asking:

5.3. Why do women smoke?

Until after World War II smoking tobacco was more or less a prerogative of

men. Women smoked in secret, and women who smoked were considered eccentric, belonging to the artistic scene, or abnormal. Women began smoking more openly during the war, and increased their smoking behaviour through the 1960's (Orlandi, 1986). Smoking went hand in hand with the growing independence of women and their entry into professional life. As long as smoking for women was considered as socially unacceptable, the rates for men and women were divergent (Waldron, 1991), that means that social disapproval inhibited women's smoking. The entrance of women into professional life with the increasing stress, entering the 'chef étages' of management, encouraged women to smoke. The positive effects of tobacco in relieving stress, reducing anxiety and negative effects, at the same time enhancing pleasure, and to relax, to combat depression, made differences in smoking ratio between men and women negligible. Another important aspect for women is the experience that smoking is used in controlling body weight (Gritz et al., 1989; Pomerleau et al., 1991).

Unfortunately some women continue to use tobacco during pregnancy. Prenatal smoking is already a risk factor. Many studies have been published about smoking during pregnancy, a topic which has drawn attention since 1957. It has become evident (Simpson, 1957) that there is a significantly lower birth weight for infants born to mothers who continued smoking, in comparison with mothers who did not smoke. Fortunately the percentage of mothers who continue smoking after learning these facts is decreasing; the figures show a certain dependence on level of education, age, race and origin, as well as on marital status (Floyd *et al.*, 1993). The major health effects of prenatal and postnatal smoking are intrauterine growth retardation, preterm delivery and infant respiratory infections. Exposure of babies to passive smoke, causes an increased rate of pneumonia, bronchitis, tracheitis, laryngitis, and Sudden Infant Death Syndrome (SIDS). So, the problems of tobacco consumption by pregnant women justify any effort for its cessation (Fisher *et al.*, 1993).

6. HEALTH HAZARDS OF TOBACCO

The appreciation of tobacco for human consumption in history has had its ups and downs (fig. 1). Periods of applause alternate with periods of condemnation. The pharmacological effect is quite clear: the fatal dose in a 50 kg human is close to 40 mg nicotine orally (Keller, 1979). In the Western World the perception of tobacco by the general public is becoming increasingly negative. In the U.S. this is due to the standpoint of the U.S. Surgeon General (SGR) who changed his position against nicotine, the main alkaloid of tobacco, during the last quarter century. In 1964 the SGR concluded in his report that 'in medical and scientific terminology the practice (of smoking) should be labelled as habituation to distinguish it clearly from addiction, since the biological effects of tobacco, like coffee and other caffein-containing beverages are not comparable to those produced by morphine, alcohol, barbiturates, and many other potent addicting drugs'. The basis for this distinction was the definition, which

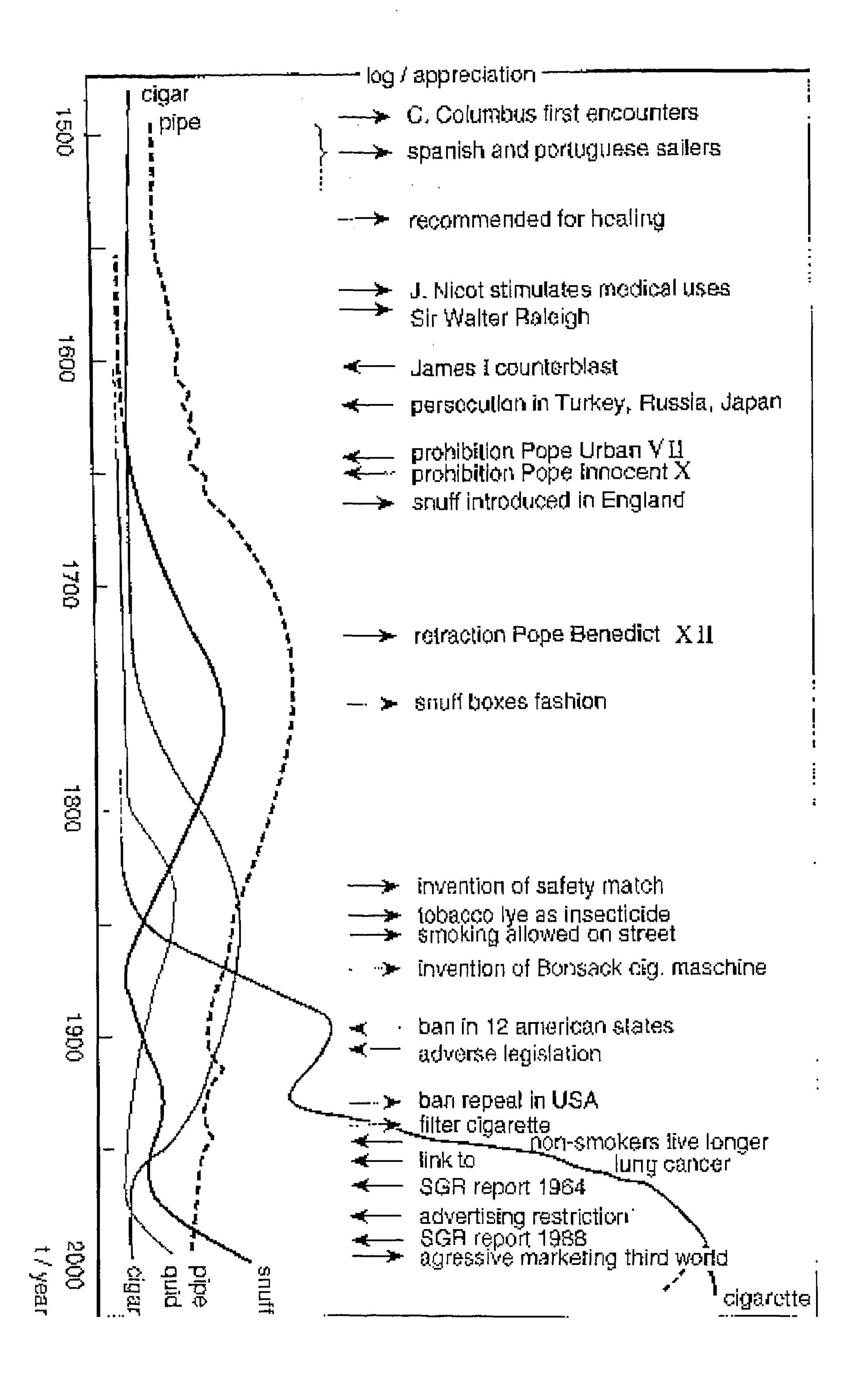


Fig. 1. An attempt to visualise the changing appreciation of the different tabacco products during history. Promotion of tobacco use is indicated by an upward arrow (1), discouragement and prohibition by a downward arrow (1).

the WHO gave for addiction 'a state of periodic or chronic intoxication produced by repeated consumption of a drug'; its characteristics include:

- (A) an overpowering desire to continue taking the drug,
- (B) the tendency to increase the dose,
- (C) a psychic and physical dependence on the effects of the drug,
- (D) detrimental effects on the individual and society.

In contrast, habituation was defined as 'a condition resulting from the repeated consumption of a drug'; its characteristics include:

- (A) a desire, but not a compulsion, to continue taking the drug for the sense of improved well-being which it engenders,
 - (B) little or no tendency to increase the dose,
- (C) some degree of psychic dependence on the drug but absence of physical dependence, and hence an abstinence syndrome,
- (D) detrimental effects, if any, primarily on the individual, rather than on society.

In 1988 the SGR changed his position and declared that nicotine is as addictive as cocaine. This reclassification of nicotine as addictive rather than habituating is not scientifically viable (see Robinson and Pritchard, 1992a,b) and based on the fact that the WHO dropped the distinction between habituation and addiction, and replaced these terms by drug dependence. There is on-going discussion about the right or wrong of the arguments (Robinson and Pritchard, 1992a,b; West, 1992). The fact that non-pharmacological factors can play an important role in tobacco consumption, which is a complex behavioural process, has been neglected.

Of course, the cognitive and performance benefits enjoyed by smokers have a pharmacological base. The sensory effects, how the tobacco smoke tastes, smells, and feels to the smoker, the whole procedure of selecting and lighting a cigarette, cigar or pipe in its social context shows that smoking is a complex process involving both pharmacological and non-pharmacological factors (Robinson and Pritchard, 1992a). Smoking is therefore more accurately classified as a habit rather than an addiction. Identification as drug dependence is even characterized as a 'misconception' (Heningfied and Nemeth-Coslett, 1988) and the term nicotine addiction was also replaced by nicotine conditioning.

Nevertheless smoking cessation programs are going on in the Western World (Fisher *et al.*, 1993), with success and failures, with relapse and withdrawal symptoms, reinforcement by nicotine's euphoriant effects, pharmacological interventions, nicotine replacements (Fisher *et al.*, 1993).

According to a survey of the world literature, allergic reactions to tobacco are a proven fact (Savel, 1970; Schmidt, 1986). Most cases of allergy to tobacco have been of an asthmatic nature. Certain types of cigarettes cause allergic symptoms which are relieved when a different brand is used (Charpin, 1986; Sheldon et al., 1967). Allergic conjunctivitis is also reported after regular use of snuff (Thiel et al., 1984). The American Environmental Pollution Agency, EPA,

has recently published a study on passive smoking. According to this study, passive smoking has an especially detrimental effects on infants and children, causing asthma, bronchitis and pneumonia. Passive smoking is tied to vitamin C loss.

Smoking is like Russian roulette: one third of the population is not affected (J. Robertson, pers. comm.) and nobody knows whether he belongs to this fraction. Mortality from tobacco in developed countries has a genetic background. Genetic analysis of smoking behaviour using the PNAS Twin Register showed a concordance for smoking that was higher among monozygotic twins than among dizygotic twins (Carmell, 1992). These data suggest genetic influence on smoking and stopping smoking. The authors conclude that there were modest genetic influences on lifetime smoking practices. This is in agreement with the new American studies which indicate that more than one-third of all regular smokers will be killed by the habit, and about half of those killed by it will still be in middle age (Peto, 1992).

Researchers found that cigarette smokers have a higher level of DNA adducts than non-smokers, and that there is a linear relationship between adduct levels and the daily or lifetime cigarette consumption. People who have given up smoking for at least five years have adduct levels similar to those of non-smokers (Phillips et al., 1988). It is clear that DNA binding of the putative carcinogens is closely related to dose. An Anglo-Dutch team of scientists believe that they have discovered a key to the cause of most types of lung cancer. They found a change in the genetic material of lung cancer patients that suggests the disease may appear after a protective gene is lost (Highfield, 1987).

And finally: the first warnings have been given that smoking may also damage sperm (Katz Miller, 1992).

In contradiction to the general health hazard attributed to tobacco products is the most recent report on the therapeutic effect of nicotine, an intriguing concept in view of the negative health consequences attributed to cigarettes (Hanauer, 1994). Starting from anecdotal reports suggesting that smoking may improve the symptoms of ulcerative colitis, a group of British and Swedish scientists provided further evidence of a beneficial effect of nicotine on this inflammatory bowel disease (Pullan et al., 1994): a supplemental six week treatment for ulcerative colitis using transdermal nicotine patches showed a statistically significant improvement. The mechanisms of life-long smoking and the effect of nicotine on this disease remain elusive.

7. TOBACCO AND POLITICS

Tobacco has become a political issue (Fritschler, 1983), not only because of its medical effects, but also as an economic and tax problem.

Cigarette consumption provides governments all over the world with one of their biggest and most reliable sources of revenu. In modern times tobacco taxes provide a healthy contribution to the balance of payments, they help development in the Third World countries where tobacco is grown (Muller, 1978). In purely economic terms, the political benefits of cigarettes outweight their social costs (Taylor, 1984). This is not only a present-day situation, but it occurred all through the 19th century. If one has a look in the British Parliamentary Papers, which report on the select committee activity on the tobacco trade of, for example, 1844, a volume of 661 pages in folio format, the topics of concern are: trade adultery, smuggling, taxation of tobacco and snuff, the seizure of tobacco by the coast guard. Tobacco is considered as 'an article of consumption', which is a strong argument in the discussion of the elected representatives for 'reduction of duty on tobacco' (Tobacco, 1844).

World wide, tobacco products are highly taxed and there is a tendency to use tax increase as a means of public health policy, as e.g. to enforce a yearly dropping of tobacco consumption by about 3% with the result that in California the cigarette smoking rate since 1974 is slightly lower than in the U.S. as a whole (Breslow and Johnson, 1993). Emphasis is laid on the aim to create a social environment that discourages the use of tobacco.

On the other hand state revenu will drop with reduced tobacco consumption. Tobacco taxes in many countries are a significant part of the state indirect income. The tobacco manufacturing industries react to the anti-smoking campaigns with more and more sophisticated advertising, trying to find a way out of the legal restrictions some states create through pressure from the anti-smoking lobby. One way out of the constantly decreasing market in industrial countries (where the reduction of tobacco consumption by men is partly compensated for by an increasing consumption of the female part of the population) is by entering markets in developing countries. As a result, the tobacco consumption in the world market is still increasing.

The recent deal of the attorney general of nearly 40 states of the U.S.A. with 4 big cigarette industries by which the companies pay about \$ 368.6 billion over the next quarter century in compensation, with the promise to drastically alter of the marketing strategies may be a milestone with respect to the appreciation of tobacco in the western societies. But Congress still has to approve the deal.

8. THE PROSPECTS OF TOBACCO IN HUMAN SOCIETY

The future acceptance of tobacco products, mainly concerns cigarette consumption, which absorbs about 85% of the world tobacco leaf production (FAO, 1989), with an increase of 1.6% per year between 1980 and 1987. The future is the result of the demand and economic significance of tobacco, as the most widely grown non-food crop, which is produced in more than 100 countries of which 78 are developing countries.

8.1. Future demands

As a result of technological improvements and rising productivity, the world area under tobacco was reduced by 10% between 1976 and 1987 to 4.3 millon hectares. Nevertheless production increased by 17% to 6.2 million tons during that time.

The area devoted to tobacco represents only a very small proportion, 0.3%, of the arable and permanent crop area of the world, compared with 9-16% used for food grains, and more than 2% for cotton, and 0.7% for coffee. Of course, the percentage of arable land under tobacco is different in the various countries from zero to 1% in Japan and 4.3% in Malawi.

One can ask the question, why tobacco still has this significant importance in the world economy, and may continue to have in the future, whereas the negative effects on human health are evident. There are several factors that determine the economic significance of tobacco in the future (FAO, 1989): tobacco generates large-scale employment, it contributes considerably to agricultural income, it is in many countries the most profitable crop, it contributes to foreign exchange earnings; even in the U.S. tobacco export earning in 1987 represent about 4% of the total foreign exchange earning from agricultural products. Tobacco is perhaps the most labour intensive of all field crops. In Malaysia it takes about 250 labour-days to grow and harvest one hectare of tobacco. Almost as much time goes into curing, grading, and sorting the tobacco once it is off the field (Muller, 1978). Tobacco manufacturing provides employment for a large labour force: from 2-6% of the total net value added to all industrial output in het developing countries, and about 1% in the developed countries. This means that tax revenues are an important source of governmental income, for example 3.5% in India to 41.3% of the total governmental tax revenue in Haiti. In the U.S.A. in 1989 tobacco tax revenue was \$ 9.4 billion, representing some 11% of all excise tax collected in that year. In the long term, prospects to the year 2000 suggest that tobacco and tobacco products will retain considerable economic significance.

In 1990, the Secretariat of the FAO prepared a report on 'Tobacco supply, demand and trade projections 1995 and 2000' (FAO, 1990), which predicts an annual production increase of tobacco leaves between 1984/86 and 2000 of 1.9%! The global consumption is expected to increase at about 1.9% annually! In terms of per capita consumption per adult on the global level it will increase from 1.85 kg in 1984/86 tot 1.86 kg in the year 2000. While the individual consumption in developed countries will fall in the period considered from 2.48 kg to 2.21 kg in the year 2000, in developing countries the increase will be from 1.59 to 1.75 kg. If these projections are accurate this will mean an annual deficit of about 185,000 tons of tobacco by the year 2000 or equal to 2% of the projected global demand. Production will react to this shortage with a new leafsaving technology and a reduction of the tobacco content of individual cigarettes. Other factors which could also reduce the gap are: any increase of the fiscal load on tobacco products, the increasing proportion of filter-tipped cigarettes, and the intensification of the anti-smoking campaigns. Consumption could also be influenced by new tobacco varieties produced by breeding (Grunewaldt, 1986) or eventually constructed by genetic engineering. These could have a higher or lower (Sengbusch, 1931; Valleau, 1949) nicotine content, so that the smoker can make a choice between reaching the same pharmacological effect with a greater number of cigarettes of lower nicotine content, due to demethylation of nicotine to nornicotine (Koelle, 1965), or by a reduced number of cigarettes, manufactured using tobacco with a higher nicotine content, resulting in a pharmacological effect in a shorter period of smoking.

8.2. Anti smoking campaigns

The future of tobacco in human society will be influenced by the non-smoking fraction of the population partly because of an increasing awareness of passive smoking. Alternatives are alreay on the market; these not only eliminate passive smoking but may also assist people to give up smoking. Nicotine patches (Belasco, 1993) deliver a steady dose of nicotine through the skin, and provide enough of the drug to stave off physical withdrawal symptoms. Other expedients to wean addicted persons from smoking are methadone derivaties; chewing gums, called 'Nicorette', which release nicotine steadily; or a nose spray with nicotine which is absorbed faster by the mucous membrane of the nose, resulting in a reduction of 26% of smokers within six months. The disadvantage is that cigarette addiction is replaced by spray addiction for half of the spray users (Lomans, 1994).

The ban on smoking on national flights shorter than six hours in the U.S. is the first step, the total ban of Northwest Airlines on its 1400 national flight, is the next one of the many types of anti-smoking strategies coming up. Interestingly, two American business men have started an airline called 'Smokers Express', organized as a club, so that on board a closed society is formed to which the smoking ban is not applied, and the traveling business men are in a good mood again.

The Chinese have discovered child power to fight smoking. The People's Republic of China is one of the most tobacco-addicted population in the world, with about 250 million smokers, in 1984 90% of them males. The ability of children to manipulate their parents has been successfully used in an antismoking campaign in primary schools (Holden, 1993).

Smokers are on the defensive against the ever increasing tobacco taxes, which have increased in the U.S. more than five fold since 1980, contributing both to a large decline in overall tobacco consumption and to a switch by some smokers from tax paid tobacco to smuggled products. There is a big campaign by the tobacco industries to decrease tobacco taxes because smuggling is out of control. For example, the statistics from Canada show a cigarette export increase in 1993 vs 1992 of 80%. But – more than 80% of the cigarettes are smuggled back into Canada and sold tax-free under the counter, whereas the domestic sales between July 1992 and July 1993 decreased by 26% (Globe and Mail, Toronto, August 21, 1993).

8.3. Smokeless tobacco

With 'No Smoking' signs in public buildings we are on the way to becoming a smokeless society. But this does not mean a society without tobacco. An alternative already on the way is the so-called 'smokeless tobacco', including chew-

ing tobacco and snuff, which has increased at an annual rate of 11% since 1984 (Rosen, 1989; River, 1987). In the U.S.A. there are about ten million users of smokeless tobacco, about 3 million of them under the age of 21. Between 1978 and 1984 the sales of chewing tobacco rose 8% and of snuff by 55% (Conally et al. 1986). Nicotine is easily absorbed through the mucous membranes of the mouth or the nose, and reaches the blood as quickly as with cigarette smoking (Shaeffer and Henderson, 1985).

Strangely enough approximately 40% of the users of snuff think there is little or no harm to one's health from using smokeless tobacco products (Orlandi and Boyd, 1989; Rosen, 1989), which results in an increasing smokeless tobacco use in the high school population (more than 17%). Fortunately, as the smokers tobacco users age, the aesthetic aspect, the spitting habits of smokeless tobacco users, make its socially unacceptable. Because of the social unacceptability, health professionals fear that the smokeless tobacco users will switch back to cigarette smoking (McCarthy et al., 1986), to satisfy their addiction for nicotine.

Peer pressure usually causes students to try smokeless tobacco: friends, and advertisements by sporting heroes tempt them, but teachers do not encourage it (Rosen, 1989).

8.4. Weakened tobacco

Largely unexplored are the possibilities of tobacco admixtures. Certain plants are useful in reducing the effect of tobacco, or acting as substitutes. There are several indigenous species of *Nicotiana*, which the aboriginal inhabitants of North America dried and utilized, and in some instances cultivated (Saunders, 1978). Their customary 'smoke', however, was not pure tobacco, and in the precolumbian days it was quite different from the 20th century commercial species. They preferred a combination with other material, which resulted in a weakened effect of tobacco. Those mixtures were already known to the plainsmen, trappers and settlers in the fur trade days and consisted of tobacco with dried leaves or bark of certain other plants. The most important admixed ones are (according to Saunders, 1978):

- 1. Silky cornel (Cornus serina L.), a shrub of wetlands, with purplish branches, underleaf surface with silky hairs.
- 2. Red dogwood (Cornus stolonifera Michx.), similar to the above one, less hairy, spreading by running suckers.
- 3. Bear-berry (Arctostaphylos uva-ursi Spreng.), evergreen vine, astringent berry, on rocks and sands.
 - 4. Sumac (Rhus glabra L.), with smooth pinnate leaves.

In the case of the first two plants, the scraped inner bark was the part which was used; in the last two, the leaves were used. The foliage of Manzanita and Arrow-wood (species of *Viburnum*) sometimes found favour. The ingredients were first thoroughly dried either in the sun or over fire, then rubbed and crumbled between the palms of the hands, hence the French applied the name bois roulé

to such smoking material. Though some tobacco was used in the make-up, it was frequently omitted – one or more of the non-narcotics being consumed alone (Saunders, 1978).

8.5. The safe cigarette

A recent development has been the effort to produce a less hazardous or 'safe' cigarette (Gori, 1980). The intention is to create a 'more healthy' cigarette, using current techniques for reducing the quantity of smoke emission as well as its specific pathogenic activity, although consumers' acceptance of smoke reduction and modifications are limited (Russell, 1991). Technically it is possible to reduce the particulate phase, which includes water, nicotine and other alkaloids, condensed particles, or pyrolysed or distilled molecules, and varying amounts of volatile compounds, dissolved in the particles. Ways to reduce the total particulate matter of smoke are: reduction of the amount of tobacco per cigarette, changing the tobacco characteristics, processing (expanded and freeze-dried) tobacco, addition of extenders (which dilute tobacco with inert material), artificial tobacco substitutes (clays or carbonates, which provide bulk), blend additives (e.g. sugar, fruit juices, menthol, lemon, essential oils, vanillin, and other fragrances), increase of the paper porosity (which can increase the static burning rate, so reducing the number of puffs, the air speed and the temperature gradient in the cigarette), and finally the widely introduced filtration by cellulose acetate, charcoal or magnesium silicate.

Today filter-cigarettes constitute the majority of the sales. They have to a large extent replaced unfiltered cigarette, are usually about 70 mm long and contain a blend of flue-cured, burley, oriental and Maryland tobaccos. The classic unfiltered cigarette produces 2.4 to 3.0 mg nicotine in the smoke, and 35 to 40 mg tar. Filters in use in 1986 resulted in a reduction of the nicotine level to about 0.9 mg, and of tar in a range of between less than 1 and 29 mg (Reynolds, 1988). This was achieved by improving the filter material and by the blend which included substantial levels of reconstituted tobacco sheets. This reconstituted tobacco is produced by extracting the tobacco with water. The cellulose fibers of the tobacco are then used to form a base sheet to which the liquid extract is applied. Filter-tipped cigarette brands on the market make up, at the present moment, about 95% of all cigarettes. Reconstituted tobacco is used in virtually every cigarette brand on the market. The introduction of more porous cigarette paper occurred in the early 1960's and in the late 60's the use of expanded or 'puffed' tobacco. The early 70's saw the emergence of the ventilated filter tips, with perforations of the filter wrappers, which resulted in an air dilution of the smoke. Filter ventilation also diminished the amount of tobacco burned during a puff, and decreased tar and nicotine content (Reynolds, 1988). The limitations of these safe cigarettes from the point of view of the smoker, are: the decrease of nicotine, when the particulate fraction is reduced. So, reduction of the known and expected effects of this alkaloids may be compensated by increasing the number of cigarettes consumed, or deeper and more efficient inhalation patterns of the smokers.

Since efforts have failed to substitute tobacco by burning other natural or processed plant material, like sunflower, rhubarb, lettuce, chestnut, beech, *Eucalyptus*, fermented *Tussilago* leaves, cornstalks, or cocoa bean hulls, the consumers preference has been victorious.

The evolution of the cigarette has resulted in a new product: the so called New Cigarette (Reynolds, 1988). Its design is to produce smoke and tobacco taste by heating, rather than burning tobacco. It is lit and smoked similar to other cigarettes, but it does not burn down to a butt, nor does it produce loose ash. It consists of two section (Reynolds, 1988): (1) the front-end piece, containing an insulated carbon heat source, and tobacco, which fits into an aluminium capsule containing flavor and glycerol; (2) the mouth-end piece, containing a two-part filtration system. The heat passes through and volatilized the natural tobacco flavour from a tobacco roll that surrounds the capsule. The vapour then passes through a tobacco-paper filter, which imparts additional tobacco flavour. The vapour is cooled within the tobacco-filter, allowing it to condense and form an aerosol that contains the particulate and vapour phase of the mainstream smoke. Finally the smoke passes through a polyethylene filter. Because the tobacco is not burned, the side-stream smoke is greatly reduced, in favour also of the non-smoker. Investigations of the smoke condensates show that both the mainstream and sidestream smoke were not genotoxic in vitro and in vivo toxicity profiles, compared with a traditional reference cigarette.

9. THE RISE OF TOBACCO AS AN EXPERIMENTAL PLANT

The decline of appreciation of tobacco in the Western World as a material for smoking, is contrasted by the rise of tobacco as an experimental plant. Among the Solanaceae *Nicotiana* is the most used experimental plant for tissue culture and in incompatibility research. For the latter it is most convenient that *N. alata* Link and Otto is self-incompatible and *N. tabacum* is self-compatible. One of the reasons for the increasing use of tobacco plants for research is the fact that they can be reproduced sexually by seeds, and asexually by cuttings.

The rise of tobacco as an experimental plant was initiated by its laboratory use in virology, e.g. for the isolation and characterization of TMC (tobacco mosaic virus), and whole plant physiology, competing only with tomato, maize and to a lesser extent, *Arabidopsis* and *Petunia*. Tobacco is even becoming a possible candidate for the production of edible proteins, so that tobacco farming could provide a rich, low-cost protein source. Moreover, tobacco protein has the potential to serve as a foaming or emulsing agent in processed consumer products like ice cream, salad dressings, and whipped dessert (Anon., 1991).

10. CONCLUSION

At the end of the evolution of tobacco as a companion of a non-unessential part of human society, we see two diametrically opposed camps: the anti tobacco-smoking group, including a large proportion of the population in North America and northern Europe who have quit smoking tobacco (Warburton, 1992), also defending the enforced passive smokers from health hazards on one side; and the active smokers and their lobby on the other side, claiming nicotine to be a low risk substance in terms of acute and chronic toxicity, improved general attentional processing capacity, and a better immediate memory and information retrieval, as an elevated endurance and a positive effect enhancement (Warburton, 1989, 1990, 1992).

Let me summarize the account of the acceptance of tobacco products in human society, by another story, which I was told recently (1993) in Qaanaq in northern Greenland.

An Inuit went to the Thule Air Base, walking through the drums of bombs under a sign saying 'No Smoking'. He took out his pipe made from walrus bone, and started to put tobacco in the pipe bowl, which he scratched together from the inner pocket of his icebear jacket, where he kept all his valuables: pipes, tobacco, matches, softened cartridges for his rifle, his knife, harpoon, points, coins. When he lit the pipe, it exploded. He hurried to his little family igloo and carefully closed the small entrance with a snow block. He took his other pipe out of his pocket and started to tell his wife: 'Listen, these Americans are tough boys, they caught me smoking among the bombs. And one of the guards on duty must have seen me and shot my pipe bowl right from under my nose'.

And he finished loading his pipe and lit his second pipe, which was a bit older than his favorite one, – with the effect that this time not only did the tobacco pipe explode but the whole igloo flew away.

Guess, what was in the tobacco mixture?

ACKNOWLEDGEMENTS

For help with the collection and the evaluation of literature I thank: S.Balabanova (München), P.F. Ditges (Bonn), L. Feldman (Amherst), C. Fletcher (London), W. Jorde (Mönchengladbach), M. Macioti (Brussels), D. Pollock (London), W.S. Pritchard (Winston-Salem), A.J. Robertson (Liverpool), H. Schadewaldt (Düsseldorf), D.M. Warburton (Reading).

For reading the draft manuscript and valuable suggestions I thank Prof. J.F. Jackson (Glen Osmond), and David Symon (Adelaide) and an anonymous referee.

I would like to thank Dr. Barbara Parkinson (University of Witwatersrand, Johannesburg) for correcting the English text.

- Albrecht, C.F. and E.L. Theron Smoking, oncogenes and human lung cancer. South Afr. Med. J. 73, 406-408 (1988).
- Alfieri, A. Les insectes de la tombe de Tutankhamon. Bull. Soc. Entomol. Egypte 24, 188–189 (1931).
- Andersen, R.A. Assessment of burley and dark tobacco alkaloids during storage, aging and fermentation. In: H.F. Linskens and J.F. Jackson (eds.), Mod. Meth. Plant Analysis 15, 153–161 (1994).
- Anon. Tobacco is nutritious says plant geneticists. Tab. Int. 192 (10), 7, June 1, 1990. Cited in Tobacco Abstracts 36 (1), 7 (1991).
- Ashton, H. and R. Stepney Smoking, psychology and pharmacology. Tavistock Publications, London, New York (1983).
- Baker, H.G. Plants and civilization. McMillan, London (1975).
- Balabanova, S., F. Parsche and W. Pirsig First identification of drugs in egyptian mummies. Naturwissenschaften 79, 358 (1992).
- Balabanova, S., F. Parsche, G. Bühler and W. Pirsig Was nicotine known in ancient egypt? Homo 44, 92-94 (1993).
- Belasco, L. All about those nicotine patches. Good Housekeeping, July, p. 181 (1993).
- Benowith, N.L. The human pharmacology of nicotine. In: H.D. Cappell (ed.), Research advances in alcohol and drug problemes 9, 1–52 (1987).
- Bergmark, M. Lust und Leid durch Drogen. Aberglaube und Wissenschaft in der Geschichte der Drogen. Wissensch. Verlagsges., Stuttgart, pp. 153-158 (1958).
- Böse, G. Und es wird doch geraucht. Eine kleine Kulturgeschichte des Tabak. Bachem, Köln (1965).
- Breslow, L. and M. Johnson California's proposition 99 on tobacco, and its impact. Annu. Rev. Publ. Health 14, 585–604 (1993).
- Carmell, D. Genetic influence on smoking a study of male twins. N. Engl. J. Med. 327, 829–833 (1992).
- Charpin, J. Allergologie 2e ed., Flammarion-Medicine-Sciences, Paris (1986).
- Colombo, F. Historie dale' amiraglie Christoforo Colombo, Venice (1571).
- Conally, G.N., D.M. Winn and S.S. Hecht The remergence of smokeless tobacco. N. Engl. J. Med. 314, 1020–1027 (1986).
- Eckholm, E. Cutting tobacco's toll. Worldwatch paper n. 18 (1978).
- FAO The economic significance of tobacco. FAO economic and social development paper n. 85, Food and Agriculture Organization of the United Nations, Rome (1989).
- FAO Tobacco: supply, demand and trade projections 1995 and 2000. FAO economic and social development paper n. 86, Food and Agricultural Organization of the United Nations, Rome (1990).
- Ferrence, R.G. Deadly fashion. The rise and fall of cigarette smoking in North America. Garlane Publ. Inc., New York, London (1989).
- Fisher, E.B., E. Lichtenstein, D. Haire-Joshu, G.D. Morgan and H.R. Rehberg Methods, success and failures of smoking cessation programs. Annu. Rev. Med. 44, 481–513 (1993).
- Floyds, R.L., B.K. Rimer, G.A. Giovino, P.D. Mukken and S.E. Sullinva A review of smoking in pregnancy: Effects of pregnancy outcomes and cessation efforts. Annu. Rev. Publ. Health 14, 379-411 (1993).
- Fritschler, A.L. Smoking and politics. Policymaking and the federal bureaucracy. Prentice-Hall, Englewood Cliffs, N.J. (1983).
- Gilbert, D.G. Paradoxical tranquilizing and emotion-reducing effects of nicotine. Psycholog. Bull. 86, 643-661 (1979).
- Gori, G.B. Less hazardous cigarettes, theory and practice. In: G.B. Gori and F.G. Bock (eds.), A safe cigarette? Banbury Report, Cold Spring Harbor Laboratory, Cold Spring Harbor (1980).
- Gottsegen, J.J. Tobacco, a study of its consumption in the United States. Pitman Publ. Co., New York, Chicago (1940).

- Grimé, W.E. Ethno-botany of the black americans. Reference Publications, Inc. Algonac, Mich. (1979).
- Gritz, E.R., R.C. Klesges and A.W. Meyers The smoking and body weight relationship: implications for interventions and postcessation weight control. Ann. Behav. Med. 11, 144–153 (1989).
- Grunewaldt, J. Nicotiana, Züchtungsforschung und Züchtung. Beiträge zur Tabakforschung 13, 103–120 (1986).
- Hamilton, A.E. This smoking world. Methuen and Co, London (1928).
- Hanauer, S.B. Nicotine for colitis the smoke has not yet cleared. N. Engl. J. Med. 330, 856–857 (1994).
- Hegnauer, R. Chemotaxonomie der Pflanzen, Vol. 6, pp. 410-413, Birkhäuser, Basel (1973).
- Hennningfield, J.E. and R. Nemeth-Coslett Nicotine dependence: interface between tobacco and tobacco related disease. Chest 93, 37S-55S (1988).
- Herks, J.J. De geschiedenis van de Amersfoortse tabak. Economisch en sociaal-historische onderzoekingen, Vol. 5, M. Nijhoff, Den Haag (1967).
- Highfield, R. Protective gene clue to all major types of lung cancer. Daily Telegraph, December 11 (1987).
- Holden, C. Fighting smoking with child power. Science 260, 1718 (1993).
- Horton, P. Revision of Nicotiana. J. Adelaide Bot. Gard. 3, 1-56 (1981).
- Katz Miller, S. Warning: smoking may damage your sperm. New Sci. 17 oct., 13-14 (1992).
- Keller, R.F. Toxins and teratogenes of the Solanaceae and Liliaceae. In: A.D. Kinghorn (ed.), Toxic plants. Columbia University Press, New York, pp. 59–82. (1979).
- Kneist, W. Rauchen oder Gesundheid. Ein kulturhistorischer Rückblick. Z. ges. Hygiene 27, 477–480 (1981).
- Knobloch, H. Berliner Grabsteine. Mogenbuch, Berlin (1991).
- Koelle, G. Der Gendosiseffekt beim Nikotinabbau des Tabak. Der Züchter 35, 222-228 (1965)
- Koenig, P. About some of the oldest documents referring to the tobacco. Der Tabak 1 (2), 135-147 (1938a).
- Koenig, P. The position of the tobacco plant in botany. Der Tabak 1 (2), 198-225 (1938b).
- Layer-Lescot, M. Feuilles et fleurs. In: La momie de Ramses II, Editions Recherche sur la civilisation. Paris, p. 182-191 (1985).
- Lescarbot, M. Nova Francia. London (1609).
- Linné, C. von Species Plantarum. Stockholm (1753).
- Lomans, P. Het gevecht met de cigaret. Intermediair, Studentedition n. 2, 15 (1994).
- McCarthy, W.J. and W.J. Newcomb Smokeless tobacco use among adolescents: Demographic differences, other substance use, and psychological correlates. J. Drug Addiction 16, 338-401 (1986).
- Magnen, J.C. Excitationes de tabaco (and de manna). Barbovio, Pavia (1658).
- Mattioli, P.A. De plantis epitome utilissima. Frankfort/Main (1586).
- Mothes, K. and K. Hieke Die Tabakwurzel als Bildungsstätte des Nicotins. Naturwissenschaften 31, 17 (1943).
- Muller, M. Tobacco and the third world: Tomorrow's epidemic? A war on want investigation into the production, promotion and the use of tobacco in the developing countries. War on Want, London (1978).
- l'Obel, M. De and P. Pena Stirpium adversaria nova. London (1570–1571).
- Orlandi, M.A. Gender differences in smoking cessation. Women Health 11, 237–251 (1986).
- Orlandi, M.A. and G. Boyd Smokeless tobacco use among adolescents: a theoretical overview. In: G.M. Boyd and C.A. Darby (eds.), Smokeless tobacco use in the United States, NCI Monographs n 89, pp. 5–12 (1989).
- Pearl, R. Tobacco smoking and longevity. Science 78, 216-217 (1933).
- Peterson, N. Aboriginal uses of australian Solanaceae. In: Hawkes, Lester and Skelding (eds.), The biology and taxonomy of the Solanaceae, Academic Press, New York (1979).
- Peto, R. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. The Lancet 339, 1268–1279 (1992).

- Phillips, D.H., A. Hewer, C.N. Martin, R.C. Garner and M.M. King Correlation of DNA adduct levels in human lung with cigarette smoke. Nature 336, 790–792 (1988).
- Pinner, A. Über Nicotin. Die Konstitution des Alkaloids. Ber. Dtsch. Chem. Ges. 26, 292 (1893).
- Pomerleau, O. and C. Pomerleau A biobehavioral view of substance abuse and addiction. J. Drug Issues 17, 11-13 (1987).
- Pomerleau, C.S., O.F. Pomerleau and G. Weinstein Biobehavioral research on nicotine use of woman. Brit, J. Addict. 86, 527-531 (1991).
- Pullan, R.D., J. Rhodes, S. Ganesh, V. Main, J.S. Morris, G.T. Williams, R.G. Newcombe, M.A.H. Russell, C. Feyerabend, G.A.O. Thomas and U. Säwe Transdermal nicotine for active ulcerative colitis. N. Engl. J. Med. 330, 811–815 (1994).
- Reynolds, R.J. Chemical and biological studies on new cigarette prototypes that heat instead of burn tobacco. R.J. Reynolds Tobacco Co., Winston-Salem, North Carolina (1988).
- River, R.E. Smokeless tobacco use: A dangerous nicotin habit. Postgraduate Medicine 81 (4), 89-94 (1987).
- Robinson, J.H. and W.S. Pritchard The role of nicotine in tobacco use. Psychopharmacology 108, 397–407 (1992a).
- Robinson, J.H. and W.S. Pritchard The meaning of addiction: reply to West. Psychopharmacology 108, 411–416 (1992b).
- Rose, J.E., M.C. Zinser, D.B. Tashkin, R. Newcomb and A. Ertle Subjective response to cigarette smoking following airway anesthetization. Addict. Behav. 9, 211–215 (1984).
- Rosen, M.A. Knowledge attitudes and practices of smokeless tobacco use in an adolescent population. MS thesis, School of Public Health, University of Massachusetts, Amherst (1989).
- Russell, M.A.H. The future of nicotine replacement. Brit. J. Addict. 86, 653-658 (1991).
- Saunders, C.F. Useful and edible wild plants of North America. Tutor Press, Toronto, pp. 229–231 (1978).
- Savel, H. Clinical hypersensitivity to eigarette smoke. Arch. Environm. Health 21, 146-148 (1970).
- Schadewaldt, H. Kultur- und Medizingeschichtliches über den Tabak. Medizinische Welt 18 (N.F.), 2140-2148, 2189-2202 (1967).
- Schmidt, F. Gibt es eine Allergie gegen Tabak? Allergologie 9, 435-438 (1986).
- Seibert, T. Tabak im Wandel der Zeiten. Der Deutsche Tabakrundschau 60, 173–178 (1980a).
- Seibert, T. Tabak im Wandel der Zeit. Die Geschichte des Rauchens. Tabak Ztg. 90, (37) 10–11, (38) 10–11 (1980b).
- Sengbusch, R. Von Die Züchtung von nicotinfreiem und nicotinarmem Tabak. Der Züchter 3, 33–38 (1931).
- Shaeffer, S.D. and A.H. Henderson Patterns of use and incidence of smokeless tobacco consumption in school-age children. Arch. Otolaryngology 111, 639-642 (1985).
- Sheldon, J.M., R.G. Lovell and K.O. Mathews A manual of clinical allergy, 2e ed., Saunders Co., Philadelphia–London (1967).
- Simpson, W.J. A preliminary report on cigarette smoking and the incidence of prematurity. Am. J. Obstet. Gynecol. 73, 808–815 (1957).
- Stahl, G. Was the custom of smoking known in ancient and mediaeval times? Der Tabak 1 (2), 148–166 (1938).
- Steffan, J.R. L'entomofauna de la momie. In: La momie de Ramses II. Editions Recherche sur la civilisation, Pris, p. 108-112 (1985).
- Stepney, R. The indians' revenge. World Medicine, November 28, 75-77 (1981).
- Taylor, P. The smoking ring. Tobacco, money and multinational politics. Pantheon Books, New York (1984).
- Thiel, C., A. Gierloff and K.G. Wulle Allergische Konjunktivits durch Schnupftabak. Allergologie 7, 139–140 (1984).
- Tobacco British parliamentary papers. Report from the selected committee on the tobacco trade with minutes of evidence, appendix and index. Volume XII, Session February 1–February 5, London, 661 pp. (1844).

- U.S. Department of Health, Education and Welfare Smoking and health. Report on the advisory committee of the Surgeon General of the Public Health Service. U.S. Government Printing Office, Washington D.C. (1964).
- U.S. Department of Health, and Human Services The health consequences of smoking: Nicotine addiction. A report on the Surgeon General. U.S. Government Printing Office, Washington D.C. (1988).
- Valleau, W.D. Breeding of low-nicotine tobacco. J. Agric. Res. 78, 171-176 (1949).
- Waldron, I. Patterns and causes of gender differences in smoking. Soc. Sci. Med. 32, 989–1005 (1991).
- Warburton, D.M. Nicotine, an addictive substance or a therapeutic agent? Progr. Drug Res. 33, 9-41 (1989).
- Warburton, D.M. Heroine, cocaine, and now nicotine. In: D.M. Warburton (ed.), Addiction controversies, Harwood Academic Publ., London, pp. 21-33 (1990).
- Warburton, D.M. Nicotine issues. Psychopharmacology 108, 393-396 (1992).
- West, R. Nicotine addiction: a re-analysis of the arguments. Psychopharmacology 108, 408–410 (1992).
- West-Consort for Public Health Proposition 99: The Californian Tobacco Tax Initiative (1990).
- Wilbert, J. Tobacco and shamanism in South Africa. Yale University Press (1987).