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Tobacco

ARNOLD BURGEN

Downing College, Cambridge, CB2 1DQ, UK. Email: asvb@cam.ac.uk

Tobacco use was well established among the inhabitants of the Americas when Columbus made his epic voyage. They smoked it in pipes and as cigars and also used it as snuff; it played an important role in social and religious practices. By 1550 pipe smoking was well established in Europe, to be largely supplanted by snuff in the 18th century and by cigarettes in the latter part of the 19th century. It was only proven in the 1950s that smoking was the major cause of lung cancer, which in turn, was responsible for an increasing proportion of deaths. Efforts to reduce smoking have had a limited success so far, but the overall incidence of lung cancer in the UK is now falling. Patterns across Europe are generally similar.

This is a time when there are obvious changes in public attitudes to smoking tobacco. Smoking is banned in an increasing number of public places, in restaurants, offices, trains, aeroplanes and even in public toilets. The reason for this is the evidence that smoking is a serious cause of ill-health. This seems a good moment to review the history of this habit and to produce a balanced appraisal.

History

There is no evidence of tobacco in Europe before Columbus, but in Central America and Mexico there are accounts of it in Maya and Aztec. There are clear inscriptions at Palenque of its use in religious ceremonies, both as cigars and pipes (Figure 1). At the beginning of November 1492, Columbus landed on Cuba. He sent Rodrigo de Jerez and Luis de Torres to explore inland accompanied by two natives from other islands. They found a number of villages consisting of 50 or more houses and with a total population of about a thousand, so far as they could estimate. These people accepted them as heavenly visitants and received them with all possible respect, the most important members of the community escorted them to the first hut in the village where the natives kissed the feet of the strangers and passed their hands over them to discover if they were actually flesh and blood. The two Spaniards watched their actions with amazement; they noticed that the

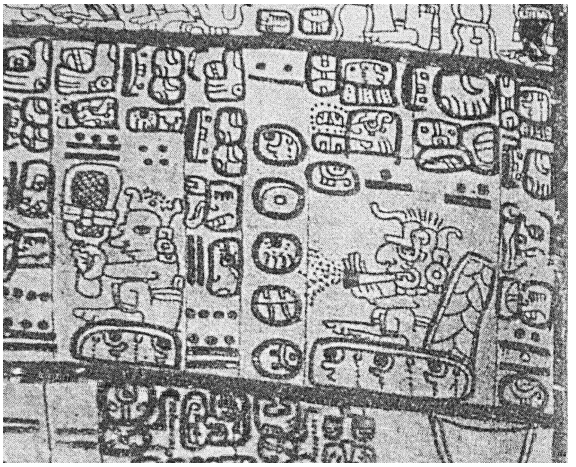


Figure 1. An inscription from Palenque in which a priest can be seen smoking a cigar.

men carried in their hands certain dried leaves, which they kindled with glowing coals and with which they apparently perfumed themselves. In order to keep the leaves alight they repeatedly held them to their mouths, alternatively blowing on them and inhaling the smoke, to the complete mystification of the Spaniards. Columbus' crew do not appear to have brought the habit of smoking with them on their return from this first voyage and the first report of the custom appears in Romano Pane's *De insularium ritibus (Concerning the customs of the Islanders)* (1497). Pane was a monk who accompanied Columbus on his second voyage in 1493 to convert the Indians. Columbus commissioned him to write a book about the religious rites and customs of the Antilles, especially San Domingo.

He says that what they call 'making Cohobba involves sniffing the smoke up through a hollow fork-shaped piece of wood that fits into both nostrils. They frequently use it as a purge. It honours the gods and it inspired the priests who were able to prophecy about the future. The cacique (priest) would inhale so much smoke that he became intoxicated and in this frenzied condition would make prophecies about victory or defeat and the state of the harvest.' Pane also says that a cake of the tobacco was given to the sick to make them vomit and rid them of evil humours.

One of Columbus' friends, Gonzalo Fernandez de Oviedo y Valdes wrote in 1526 his *Historia general y natural de los Indias,* in which he discusses Pane's account and says 'they inhale the smoke until they become unconscious and lay sprawling on the earth like men in a drunken slumber… the Indians call this weed *tobacco* … I cannot imagine what pleasure they have from this practice… They

plant the plant on their farms and inhale the smoke, for they say that if they take tobacco when their day's work is over they forget their fatigue.[11] In 1527, Bishop Bartholome de las Casas (*Histoire des Indes 1520–1559*) wrote that in Cuba 'The herb that the Indians inhale is rolled up like a sort of bundle in a dried leaf… They light one end of it and draw in smoke at the other; the effect is a certain drowsiness of the whole body accompanied by a species of intoxication, in which state they declare that they no longer feel any sense of fatigue. They have a cigar case in which the already rolled cigars are carried'.

Cortes, who landed at Tabasco, found that tobacco was burned as incense in the temples and that the inhabitants had pipes painted with figures of flowers, animals and men. The Aztec name was *picietl* or *yetl* (in Cuba *tobacco*, in Brazil *petum*), the Mexicans also used snuff. Cabral in Brazil found that they used a pipe consisting of a[11] reed inserted into a gourd the shape of a human head … the smoke when inhaled produced an intoxication … they would stagger about, roll their eyes, gnash their teeth foam at the mouth and break into a frenzied dance[11] (obviously not just tobacco!); wherever Jacques Cartier went in Canada he found the Indians smoking tobacco. Excavations have revealed tobacco pipes all over the Americas, except perhaps in the West coast areas of South America.

Another solanaceous plant, *Duboisia hopwoodii* is the equivalent to tobacco in Australia where it was used very extensively by the aborigines and contained a similar amount of nicotine.[5] The leaves are dried and then mixed with an alkaline ash so liberating the alkaloid as a base. The quid is chewed and is passed around and then parked behind the ear; it is known as *pituri.* It plays an important part in the social rites at their 'Big Talk' and feasts, and is passed round starting with the chief, the *pin'aroo*. At Cooper's Creek when friends meet they salute '*gaow gaow*' (peace) and then exchange *pituri* quids which when well-chewed are returned to behind the ear. In other parts pipes serve the same purpose.

In 1558, the use of tobacco as snuff was introduced into Europe by the Portuguese from their colony in Brazil. In 1559, Jean Nicot became ambassador of France in Lisbon. Dining with a friend Damiao de Goes, he was shown the plant growing in the garden and heard of its healing properties, for instance when applied to cancerous tumours. He tried it on a wound in the face of a friend and completely healed it in ten days.. He passed the information of its wonderful healing properties to the French court including sending it as gifts to Catherine de Medici. In a letter to the Cardinal de Lorraine[6] he says ' J'ay recouvré d'une herbe d'Inde de merveilleuse et experimentée propriété contre le noli me tangere (cancerous ulcer), et les fistules deplorées comme irrémédiables par les médicins …' Through this communication the plant and eventually its active constituent acquired their names. The number of complaints that it was said to cure was fabulous: coughs, asthma, headache, stomach cramps, gout and diseases of women as well as expelling worms and curing wounds and tumours. Nicolo

Mainardes wrote a book on its medicinal uses (translated into French by Gihory as *Instructions sur l'herbe petum, die en France l'herbe de la Reine Medicee*, 1572). Nicot did not mention smoking but was concerned solely with the medicinal properties. The botanical name *nicotiana* first appears in Liebaults' *L'Agriculture et la maison rustique* (1570), but mention of the herb had appeared earlier in the *Cruydebock* of Dodonaus Lambert (Antwerp, 1563).

John Hawkins in his second voyage in 1564–65 mentioned the natives of Florida smoking to appease hunger; smoking was taken up by the sea captains who were the first to be seen in England smoking in public for pleasure rather than for medicinal purposes. Walter Raleigh brought three Indians back to England from America who smoked and were unwilling to give up the habit. In 1585, Raleigh sent Richard Grenville to establish the colony of Virginia and in the party was Thomas Hariot, a scientist who made a scientific survey written up as *Brief and True Report of the New Found Land of Virginia: Sir Walter Raleigh's Colony of MDLXXXV* (1585). Hariot was very struck by the pipe-smoking; he says' the smoke opens up the pores and expels superfluous moisture from the body and opens all the pores with the result that the Indians enjoy better health than the civilized English settlers. We tried their way of inhaling the smoke and have had many rare and wonderful proofs of the beneficial effects of this plant'. Raleigh became an enthusiastic smoker and in a very short time pipe smoking became the vogue in England. This was not well established on the continent and Paul Hentzner from Germany who visited England in 1598 was astonished at the general use of smoking.

Not everyone was happy with this new habit and notably King James I had become very opposed and wrote *Misocapnus sive de abusu Tobacci lusus regius* in1602, and in 1604 this became *A counterblaste to Tobacco*:

> In my opinion there cannot be a more base and hurtful corruption in a Countrey than is the vile use (or abuse) of taking Tobacco. … For Tobacco was first found out by some barbarous Indians to be a Preservative or Antidote against the Pockes, a filthy disease, whereunto these barbarous people are very much subject… so that as from them was first brought into Christendome, that most detestable disease, so that from them likewise was brought this use of Tobacco, as a stinking and unsavoury Antidot, for so corrupted and execrable a Maladie, the stinking Self-fumigation whereof they yet use against that disease …
>
> And what greater absurditie can there bee, then to say that one cure shall serve for divers, nay, contrarious sortes of diseases?… such is the miraculous omnipotencie of our strong tasted Tobacco, as it cures all sorts of diseases… It cures the Gowt in the feet and which is miraculous in that very instant when the smoke thereof, as light, flies up into the head, the vertue thereof, as heavie, runs down to the little toe… To take a custome in any thing that cannot bee left againe, is most harmefull to the people of my land. Moreover, which is a great iniquitie, and against humanitie, the husband shall not bee ashamed, to reduce thereby his

> delicate, wholesome and cleane complexioned wife, to that extremitie, that either shee must also corrupt her sweete breath therewith, or else resolve to live in a perpetuall stinking torment.

The denunciation from the throne had little effect on smoking, which had taken a strong hold. The demand for tobacco resulted in Virginia being turned into a tobacco plantation. By 1620, it sent 40,000 lb of tobacco; in 1619, the cultivation of tobacco in England was forbidden and it became the staple industry of Virginia; it became a royal monopoly and through a heavy tax an important part of the royal income. James' successor, King Charles I simply increased the tax.

In Holland, smoking grew from about 1580, and in 1627, Joachim von Rusdorff noted 'I cannot refrain from a few words of protest against the astounding fashion lately introduced from America–a sort of smoke-tippling, one might call it, which enslaves its victims more completely than any other form of intoxication' (*Metamorphosis Europae*). By the middle of the 17th century it was common throughout Europe. One physician wrote 'There can be no doubt that tobacco can cleanse all impurities and disperse any gross humour … it cures cancer of the breast, open and eating sores, however poisonous and septic, goitre, broken limbs, erysipelas etc. Molière (1664) says in Tartuffe 'it is the passion of all proper people and he who lives without tobacco has nothing to live for. Not only does it refresh and cleanse men's brains, but it guides their souls in the ways of virtue, and by it one learns to be a man of honour'.

Many were not in favour a of smoking and, for instance, the Prince Archbishop of Vienna in 1657 issued a decree: 'Whereas the harmful and immoderate habit of smoking has undoubtedly been the cause of serious conflagrations, to say nothing to other damage and annoyance, with a view to suppressing this evil we do hereby command that the use of tobacco be universally forbidden under pain of severe and certain punishment'. Elector Johann Georg of Saxony proclaimed: 'be it known to all that for the future not only is smoking absolutely forbidden to soldiers and civilians alike, both in beer-house and cellars, but tobacco must no longer be sold except in apothecaries shops as ordered by a doctor's prescription' (19 May, 1653). The Chief of Police in Berlin in 1810 issued the order: 'Seeing that smoking in streets and on promenades is as indecent as it is dangerous and contrary to the character of an orderly and civilized city, the same is strictly forbidden not only for Berlin, but in Charlottenburg and the Tiergarten and may only take place in those two latter places at the doors of houses, on the part of those who sit and stand there. Anyone transgressing shall have his pipe taken from him and be punished with a fine of five thalers or corresponding imprisonment or corporal punishment'.

But tobacco became an important source of state revenue (as it remains to this day). As the Emperor Leopold held[11] for the good of Our General treasury We

have Graciously determined …to draw revenue from tobacco whether smoked or taken as snuff.'

By the 18th century, snuff taking took off in France and England and soon everyone followed, it was now the fashionable way of taking tobacco. Napoleon financed most of the costs of the army from the tax on tobacco; he did not smoke but was a great snuff taker and also a collector of other people's snuff boxes! In Prussia, the Tobacco club was the centre of intrigue, Frederick the Great was an addict; a state monopoly was set up which doubled the price. Dr Johnson said in 1773 'smoking has gone out. To be sure it is a shocking thing blowing smoke out of our mouths into other peoples mouths, noses and eyes and having the same thing done to us'. It was out of fashion even with Cambridge undergraduates in 1786.

However, Barrie says in *My Lady Nicotine* (1890): 'When Raleigh in honour of whom should have changed its name, introduced tobacco, the glorious Elizabethan age began … men who had hitherto only concerned themselves with the narrow things of home put a pipe in their mouths and became philosophers. Poets and dramatists smoked until all ignoble ideas were driven from them and in their place rushed such high thoughts as the world had not known before… The whole country was stirred by the ambition to live up to tobacco'.

Cigarettes which were known as Papelitos in Brazil, spread to Spain and France and became popular by 1850, but it was largely as a result of mechanized production, introduced by James Duke in the US in 1890, that it replaced snuff and became the most common way of taking tobacco; by 1980 in UK over 120 billion cigarettes were sold per year.

This account is just a sampling from the very rich history of tobacco, in which it can be seen that tobacco has been both an enthusiasm but also frequently a source of controversy and prohibitions.

Chemistry and biology

At the beginning of the 19th century, the science of chemistry began developing. Nicolas Vauquelin in Paris isolated the active principal of tobacco in an impure state and noted that it was an acrid tasting base that formed salts; Henry and Boutron-Charland and Posselt and Reimann, obtained it in a pure crystalline state and prepared many salts. They reported that various dried tobacco leaves contained between 3–12% of nicotine. In 1851, M. Orfila found himself investigating the mysterious death of Gustave Fougnies who died suddenly at dinner in the Chateau de Bitremont. He carried out studies of the toxicity of nicotine in the dog and proved in court at Hainault that Fougnies' death was due to nicotine. There were many accounts of the actions of nicotine in animals in the 19th century, a key one by Hirschmann, in 1863, showed that it first stimulated sympathetic nerves and later paralysed them; the follow up of this by John Langley

led in 1906 to a classic paper in which he showed that nicotine acted on nerve cells and on muscles through what he termed a 'receptive substance'.

In 1914, Henry Dale came across a substance, acetylcholine in a sample of ergot, which reproduced in animals the effects of nicotine on sympathetic ganglia (acetylcholine also produced other effects, which were like those produced by muscarine, a drug derived from the fungus, amanita muscaria, but we will not consider this further here). Later, as a result of ingenious experiments on the frog heart by Otto Loewi and experiments in mammals by Dale and his collaborators, it became clear that acetylcholine was a normal body constituent that was released when some nerves were stimulated and which then activated the cells in the organs to which the nerves were connected. The acetylcholine was a *chemical transmitter* of the effects of the nerves; this was the case in muscles and in ganglia of the autonomic nerves in which it had an effect like nicotine (elsewhere, as in the heart and secreting glands, the effects were like those of muscarine). Evidence has since accumulated that acetylcholine plays an important role in synaptic transmission in various areas of the brain. This insight transformed the understanding of the working of the brain and how drugs work on it, although it has turned out that acetylcholine was just one of a number of substances that are involved in synaptic transmission.

Intensive research in recent years has revealed much about the nature of the receptors that are sensitive to the action of nicotine. They are composed of five proteins (subunits) arranged around a central channel (Figure 2); this channel is opened when the receptor is activated by nicotine and it then allows the passage of the inorganic ions, sodium and calcium to enter the cell, leading to electrical activation of the cell and in the case of muscle to contraction. A variety of subunits have been found in the receptors isolated from different locations, so that there is not a single nicotinic receptor, but rather a family of related receptors with slightly different properties and sensitivity to drugs. For instance, the receptor in muscle is rather insensitive to nicotine and hence is not affected by the amounts of nicotine found in the blood while smoking. There is still some uncertainty about which forms of the receptors are most important in the brain, but certainly, the $\alpha 4\beta 2$ one shown in Figure 2 on the right and one in which all the subunits are of the $\alpha 7$ type are important. The effects of nicotine on many types of brain cell have been shown, but it is difficult to relate these to particular behavioural responses. Nicotine found an additional use as an insecticide and recently new insecticides such as Imacloprid have been synthesized, which are highly active on the receptor in insects but to which mammalian receptors are quite insensitive.

Nicotine boils at 259°C but with decomposition, and in tobacco smoke it is particulate in a complex mixture with other constituents. The smoke from cigarettes is usually slightly acid, and in this form very little nicotine is absorbed from the mouth, but if it is inhaled absorption can occur in the lungs. By contrast,

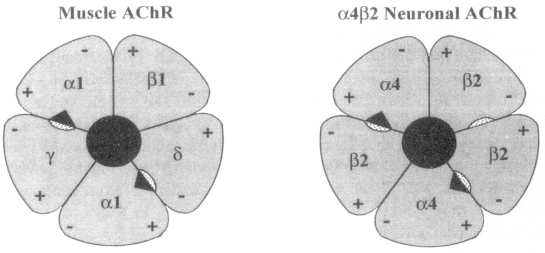


Figure 2. The arrangement of subunits in variant nicotinic receptors.

pipe and cigar smoke is more alkaline and considerable absorption occurs in the mouth; nicotine is readily absorbed in the nose from snuff. Nicotine chewing gum has been tried mainly to wean smokers of the habit but it has not been a great success because of poor absorption; it is obvious that this difficulty can be overcome, as chewing tobacco shows, by making the quid alkaline with wood ash or other alkali, but you would not get as rapid a rise in blood level as in smoking. Nicotine lasts in the circulation for up to an hour or two (the half-time is about an hour).

Why has smoking become so general an addiction? And addiction it is, as shown by the great difficulty many people have in giving it up. The usual answer people give as to why they smoke is that it relaxes and aids them when stressed or tired and improves their attention and relieves pain; there is clearly also a procedural habit in just lighting up, and the prevalence of smoking among teenagers suggests that it is part of teenager assertion. Experimental studies support the subjective assessment, and show improvement in attention, learning and in performance of some tasks, including more rapid completion of simple arithmetic and there are convincing reports of its relief of pain. One account says 'nicotine is a unique substance in that it combines performance enhancement with mood-changing properties'. Many of these effects have been reproduced in tests of animal behaviour.

Nicotine has actions other than through the central nervous system, notably on the immune system, it reduces autoimmune responses, has anti-inflammatory effects and improves some responses to infection. Some of these effects can be attributed to an increase in the secretion of ACTH and glucocorticoids.[7]

The Downside

It is a commonplace to talk of a Smoker's Cough, representing bronchial inflammation due to tobacco smoke, sometimes leading to chronic bronchitis and indeed this is a considerable cause of illness and disability, but this is not the main

concern that has arisen. In the 1940s it became noticed that there was an increase in bronchial carcinoma around the world. Previously this had been one of the rarer forms of cancer, but now it accounted for about a quarter of cancers in men and had become one of the commonest cancers. In 1922 there were 612 deaths from bronchial cancer in England and Wales, but by 1949 there were 9287, an increase of 15 fold! Similar increases were recorded in Switzerland, Denmark, Canada, Australia and the US. In looking for the reason for this, the suspicion fell on smoking. But why this recent increase? The increase in consumption of tobacco over the period had increased, but in the UK only from 1.3 to 2.0 kg/person/yr; however, in that time there was a very large increase in the smoking of cigarettes, which now dominated tobacco use. The correlation with cigarette smoking was highly suggestive, but correlations by themselves do not prove a causal connection. Richard Doll and Bradford Hill[8] set out to settle the question by looking at paired populations that were similar apart from the question of whether or not they smoked. They were able to establish that the death rate from lung cancer was increased for cigarette smokers in all age groups, but especially in the older age groups; in addition there was a clear dependence on how many cigarettes were smoked per day. If someone in the 65–74 age group smoked less than 15/day he was 2.66 times as likely to get the disease as a non-smoker, but if he smoked more that 50 per day, he was over 10 times as likely to get the disease. The careful controls and the quantitation in the correlations reported in this study were very convincing that this did show a causal connection. Since that time these results have been confirmed and extended and published in a series of reports by the British Royal College of Physicians, the US Surgeon General and elsewhere. Both cigars and pipe smoking led to a smaller increase in risk and it is not clear why cigarettes were so much worse, nor if filter tips minimized the risk. It was now generally agreed that cancer of the lung was almost entirely due to cigarette smoking and in 1980 it accounted for 11.6% of deaths in males over the age of 45 and 4.8% of deaths in women. In the later reports, evidence was produced that smoking was contributory to deaths from cancers of the oesophagus and bladder as well as to coronary heart disease and to peripheral vascular disease, so that the overall lethal effect of smoking was considerably greater than just that due to lung cancer. Tobacco smoke contains a large number of different chemical substances, but amongst them are well established carcinogens, such as nitrosamines and polycyclic hydrocarbons.

It would be expected that such a serious health situation would produce a vigorous response from responsible governments, but these have been surprisingly modest, mostly statements in government reports, some admonitory advertising, the statement on cigarette packages (SMOKING CAN KILL), gradual restrictions on smoking in public places and, in some countries, a ban on tobacco advertising.

Nevertheless, in the UK this has had a considerable effect. In 1950, 82% of adult males smoked, two thirds smoking cigarettes, but by 1998 this had declined to 36% nearly all smoking cigarettes; the corresponding figures for women were 40% in 1950, then rising to a peak by 1970 and then decreasing to 28% by 1998. During this time the sales of cigarettes had declined from 127 billion/year to 56 billion/year (− 56%) but pipe tobacco had declined much more, by–89%.

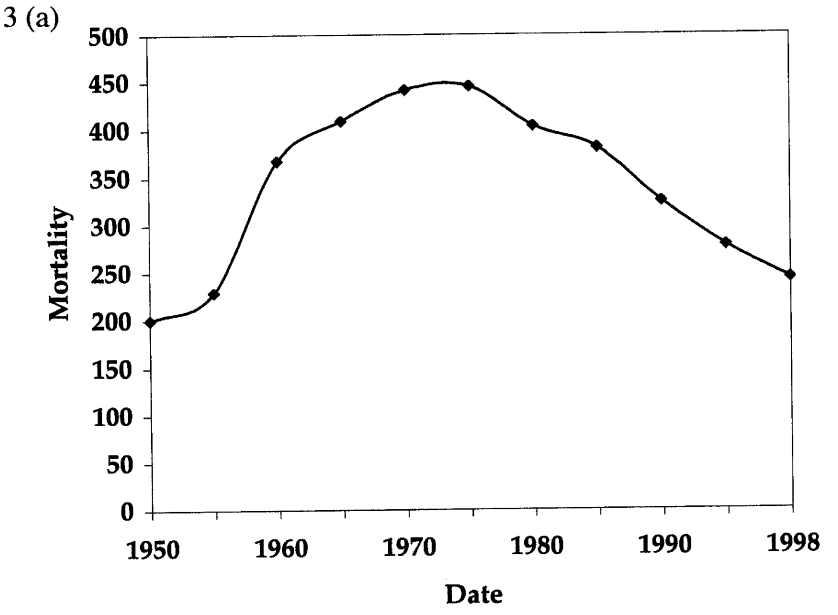
What effect had this on the incidence of lung cancer? Figure 3(a) shows the results in men aged 55–74. It can be seen that the incidence of lung cancer was rising rapidly and, by 1968, it was 2.5 times what it was in 1950, but it then began a slow decline, which still seems to be continuing. However, it is not yet quite back to the 1950 levels. The earlier rise, despite a diminishing smoking rate, is to be expected in a condition determined by chronic exposure.

Despite these 'improvements', 25% of all cancer deaths in males and 18% of all cancer deaths in females in 2002 were due to lung cancer; this is partly because the cure rate from lung cancer is still very small, whereas that from most other common cancers has greatly improved. An analysis of the tobacco habit in relation to class shows that tobacco consumption in 1996 was greater in male manual workers (39%) than in professionals (12%); unless the message gets across more effectively to manual workers, the expectation of eliminating smoking seems remote.

The incidence of lung cancer in women, which had been a tenth of that in men in 1950 has grown steadily and continued to grow past the time when it was declining in men. It may have now passed its peak and at present it is about one half of the rate in men. A matter of particular concern is the rapid development of smoking in teenagers, in girls more than boys.[9] There is no doubt that some of the deleterious effects of smoking can also affect what have been called 'passive smokers', i.e. those inhaling contaminated air in the vicinity of smokers; the banning of smoking in most public places greatly reduces this as well as reducing the nuisance to non-smokers.

How unique are these results in the UK? The pattern across Europe of male deaths from lung cancer is not dissimilar from the UK, although in some instances, the decline in cancer incidence is not as marked as in the UK.[10] The growth in female deaths is also seen in France, Belgium and the Netherlands, is especially marked in Sweden, but much less in Spain.

We referred earlier to tobacco smoking as an addiction, it is clearly a strong addiction affecting a large part of the population of Europe and seems to be still growing strongly in parts of the developing world. The measures introduced to increasingly restrict the areas where smoking is permitted are likely to put pressure on smokers that will lead to a further decrease but there is a long way to go.



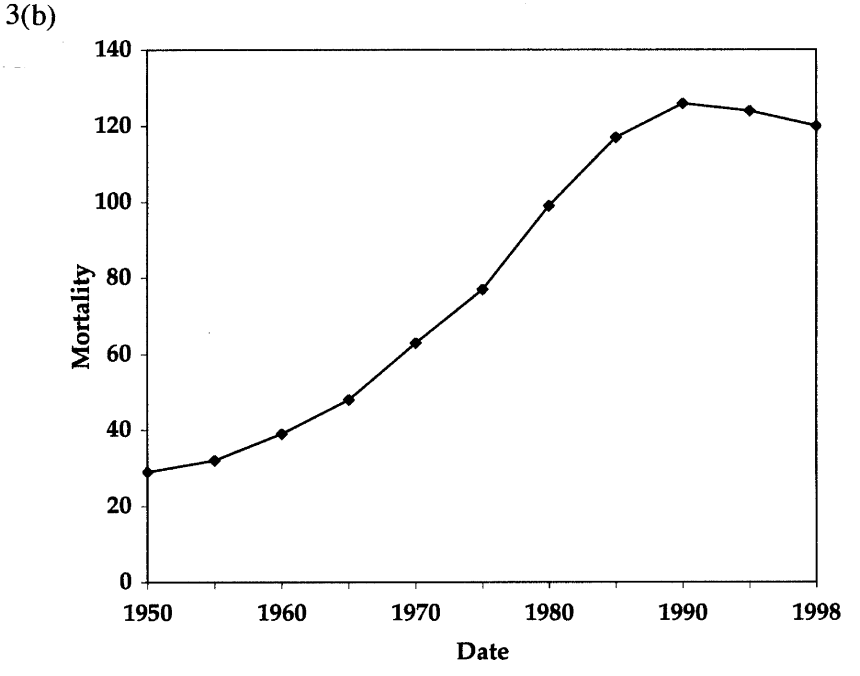


Figure 3. Incidence of deaths from cancer of the lung (per 100,000) in (a) males and (b) females aged 55–74 in the UK.

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The Upside

In a number of diseases there is evidence of abnormalities in the nicotinic receptors in the brain, these include Alzheimer's disease, Parkinson's disease, schizophrenia and some forms of epilepsy.[11] In all of these there is evidence that smoking and the administration of nicotine can be helpful, but the effects are relatively small. This has been a stimulus to research seeking better agents acting on nicotinic receptors, the analgesic action of nicotine has also encouraged the search for new agents acting in this way. A number of active compounds have been uncovered, notably epibatidine, derived from the skin of the frog, *Epipedobates tricolor*, whose chemical structure is closely related to nicotine. It is much more active than nicotine, but unfortunately it has proved too toxic to be useful, but some other synthetic derivatives have offered enough promise to go into clinical trial.[12]

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About the Author

Arnold Burgen is a former Director of the National Institute for Medical Research, London and Professor of Pharmacology at the University of Cambridge.

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