apy or when patients are unable to discontinue chronic concomitant corticosteroid use within 6 months of starting natalizumab.

Natalizumab has also been investigated for the treatment of ulcerative colitis.

◊ References.

1. Sweet BV. Natalizumab update. *Am J Health-Syst Pharm* 2007; **64:** 705–16.

Inflammatory bowel disease. The efficacy and safety of natalizumab in the treatment of *Crohn's disease* have been reviewed, including proposed mechanisms for the role of α4 integrins in the immunopathogenesis of inflammatory bowel disease (p.1697).[1,2] A systematic review[3] of controlled studies of the use of natalizumab in the treatment of Crohn's disease concluded that it is effective for induction of clinical response and remission in some patients with moderately to severely active Crohn's disease, particularly those with active inflammation or chronically active disease despite use of conventional treatment. However, this benefit must be weighed against the risks of developing progressive multifocal leukoencephalopathy.

Natalizumab is also under investigation for *ulcerative colitis*.[4]

1. Keeley KA, *et al.* Natalizumab for the treatment of multiple sclerosis and Crohn's disease. *Ann Pharmacother* 2005; **39:** 1833–43.
2. Lanzarotto F, *et al.* Novel treatment options for inflammatory bowel disease: targeting α 4 integrin. *Drugs* 2006; **66:** 1179–89.
3. MacDonald JK, McDonald JWD. Natalizumab for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 11/02/08).
4. Feagan BG, *et al.* Treatment of ulcerative colitis with a humanized antibody to the α4β7 integrin. *N Engl J Med* 2005; **352:** 2499–2507.

Multiple sclerosis. The efficacy and safety of natalizumab in the treatment of multiple sclerosis (p.892) have been reviewed, including proposed mechanisms for the role of α4 integrins in its immunopathogenesis.[1-3] Randomised controlled studies[4-7] showed beneficial results in suppressing inflammatory lesions and reducing the frequency of relapse. Subsequent review[8] of the data from the AFFIRM trial[5] and the SENTINEL study[6] demonstrated reduction of visual loss. In the SENTINEL study,[6] natalizumab was given with interferon beta, a combination that may have contributed to the development of progressive multifocal leukoencephalopathy in 2 of the study patients, one of whom died (see Infections, above). As a consequence, natalizumab is currently licensed only as monotherapy.

1. Keeley KA, *et al.* Natalizumab for the treatment of multiple sclerosis and Crohn's disease. *Ann Pharmacother* 2005; **39:** 1833–43.
2. Rice GPA, *et al.* Anti-α4 integrin therapy for multiple sclerosis: mechanisms and rationale. *Neurology* 2005; **64:** 1336–42.
3. Ransohoff RM. Natalizumab for multiple sclerosis. *N Engl J Med* 2007; **356:** 2622–9.
4. Miller DH, *et al.* A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003; **348:** 15–23.
5. Polman CH, *et al.* AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 899–910.
6. Rudick RA, *et al.* SENTINEL investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 911–23.
7. Miller DH, *et al.* AFFIRM Investigators. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. *Neurology* 2007; **68:** 1390–1401.
8. Balcer LJ, *et al.* AFFIRM and SENTINEL investigators. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology* 2007; **68:** 1299–1304.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Tysabri; ***Cz.:*** Tysabri; ***Gr.:*** Tysabri; ***Port.:*** Tysabri; ***UK:*** Tysabri; ***USA:*** Tysabri.

Neroli Oil

Aurantii amari floris aetheroleum; Aurantii Amari Floris Aetheroleum (bitter-orange flower oil); Aurantii Amari Floris Etheroleum; Azahar, aceite esencial de; Bitter-Orange Flower Oil; Esencia de Azahar; Essência de Flor de Laranjeira; Karčiavaisių citrinmedžių žiedų eterinis aliejus (bitter-orange flower oil); Keserű narancs virág olaj (bitter-orange flower oil); Neroli aetheroleum; Néroli, huile essentielle de; Neroliolja; Neroliölju; Olejek z kwiatu pomarańczy gorzkiej; Oleum Neroli; Orange Flower Oil; Orange-flower Oil; Silice květů hořkého pomeranče.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Neroli Oil). A clear, pale yellow or dark yellow liquid with a characteristic odour obtained by steam distillation from the fresh flowers of *Citrus aurantium* subsp. *aurantium* (*C. aurantium* subsp. *amara*). Relative density 0.863 to 0.880. Store in well-filled airtight containers at a temperature below 25°. Protect from light.

Profile

Neroli oil is used as a flavour and in perfumery. It is also used in aromatherapy. Photosensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Agua Melisa Carminativa; ***Cz.:*** Stopangin; ***Ital.:*** Controller; ***Rus.:*** Stopangin (Стопангин); ***Switz.:*** Hygiodermil; Kemeol; Oculosan.

Nerve Agents

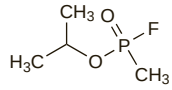
Gases nerviosos.

Sarin

GB; Sarín. Isopropyl methylphosphonofluoridate.

$C_4H_{10}FO_2P$ = 140.1.

CAS — 107-44-8.

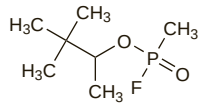


Soman

GD; Somán. Pinacolyl methylphosphonofluoridate.

$C_7H_{16}FO_2P$ = 182.2.

CAS — 96-64-0.



Tabun

GA; Tabún. Ethyl *N*-dimethylphosphoramidocyanidate.

$C_5H_{11}N_2O_2P$ = 162.1.

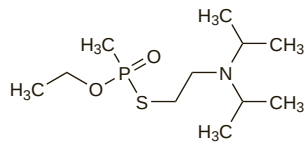
CAS — 77-81-6.

VX

Methylphosphonothioic acid S-{2-[bis(1-methylethyl)amino]ethyl} *O*-ethyl ester.

$C_{11}H_{26}NO_2PS$ = 267.4.

CAS — 50782-69-9.



Profile

The nerve agents, sarin, soman, tabun, and VX (also referred to as 'nerve gases') used in chemical warfare are extremely potent inhibitors of cholinesterase. The effects of poisoning due to these agents, and their treatment, are similar to those for organophosphorus insecticides (p.2047) but as the nerve agents have a much greater intrinsic toxicity the symptoms of poisoning are more severe. Pyridostigmine has been given prophylactically to personnel at risk from exposure to nerve agents (see p.634).

◊ References.

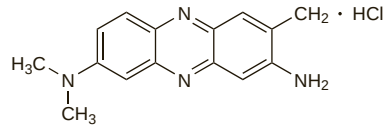
1. Ministry of Defence. *Medical manual of defence against chemical agents*. London: HMSO, 1987. (JSP312)
2. World MJ. Toxic gas trauma. *Lancet* 1995; **346:** 260–1.
3. Nozaki H, *et al.* A case of VX poisoning and the difference from sarin. *Lancet* 1995; **346:** 698–9.
4. Okumura T, *et al.* Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med* 1996; **28:** 129–35.
5. Suzuki J, *et al.* Eighteen cases exposed to sarin in Matsumoto, Japan. *Intern Med* 1997; **36:** 466–70.
6. Holstege CP, *et al.* Chemical warfare: nerve agent poisoning. *Crit Care Clin* 1997; **13:** 923–42.
7. United States Army. *Medical Management of Chemical Casualties Handbook*, 3rd ed. Aberdeen, Maryland: Medical Research Institute of Chemical Defense; 1999. Also available at: http://www.brooksidepress.org/Products/OperationalMedicine/DATA/operationalmed/Manuals/RedHandbook/001TitlePage.htm (accessed 24/07/08)
8. Weinbroum AA, *et al.* Anaesthesia and critical care considerations in nerve agent warfare trauma casualties. *Resuscitation* 2000; **47:** 113–23.
9. Anonymous. Prevention and treatment of injury from chemical warfare agents. *Med Lett Drugs Ther* 2002; **44:** 1–3.
10. Janowsky DS. Central anticholinergics to treat nerve-agent poisoning. *Lancet* 2002; **359:** 265–6.
11. Anonymous. Nerve agents. *J R Army Med Corps* 2002; **148:** 344–57.
12. Lee EC. Clinical manifestations of sarin nerve gas exposure. *JAMA* 2003; **290:** 659–62.
13. Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics* 2003; **112:** 648–58.
14. Newmark J. The birth of nerve agent warfare: lessons from Syed Abbas Foroutan. *Neurology* 2004; **62:** 1590–6.

Neutral Red

CI Basic Red 5; Colour Index No. 50040; Neutral Red Chloride; Nuclear Fast Red; Rojo neutro; Toluylene Red. 3-Amino-7-dimethylamino-2-methylphenazine hydrochloride.

$C_{15}H_{16}N_4$,HCl = 288.8.

CAS — 553-24-2.



Profile

Neutral red is used as an indicator for alkalinity and for preparing neutral-red paper. It is also used as a stain in microscopy.

It is a photoactive dye that has been tried in photodynamic therapy of recurrent herpes simplex infections, but with limited success.

Niaouli Oil

Essence de Niaouli; Gomenol.

Pharmacopoeias. In *It.*

Profile

Niaouli oil is a volatile oil, obtained by distillation from the fresh leaves of *Melaleuca viridiflora* or *Melaleuca quinquenervia* (Myrtaceae). It contains cineole and has similar actions to eucalyptus oil (p.2301). It is an ingredient of many preparations. Typical indications include respiratory tract congestion. Cajuput oil (p.2271) and melaleuca oil (p.2338) are also prepared from *Melaleuca* spp.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Gomenol; Gomenoleo; Huile Gomenolee.

Multi-ingredient: ***Arg.:*** Aseptobron; Aseptobron Ampicilina†; Di-Neumobron; Medex Rub; No-Tos Adultos; Otorinazol†; Refenax Caramelos Expectorantes; ***Braz.:*** Algice; Baldin-CE†; Canfomenol†; Gripanil†; Gripônia†; Gripsay; Killgrip†; Mentalol†; Ozonyl; Ozonyl Aquoso; Ozonyl Expectorante; Tetrapulmo; ***Canad.:*** Balminil Suppositories; ***Fr.:*** Balsolene; Biogaze†; Dinacode†; Hexaquine; Terpone; Vaseline Gomenolee; ***Ger.:*** Palatol†; ***Ital.:*** Paidorinovit; Rinantipiol†; Rinobalsamiche†; Rinofomentil†; Rinopaidolo; Rinovit; ***Pol.:*** Argol Grip; ***Port.:*** Rectopulmo Adultos†; Rectopulmo Infantil†; ***Spain:*** Broncovital†; Brota Rectal Balsamico; Pastillas Pectoral Kely; Rinobanedif; Vapores Pyt; Vitavox Pastillas†; ***Switz.:*** Liberol Bain†; Pulmex; Resorbane; ***Turk.:*** Buguseptil; Rinolar.

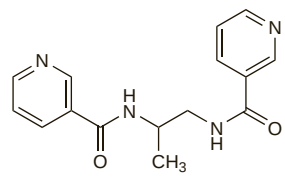
Nicaraven *(rINN)*

Nicaravén; Nicaravenum. (±)-*N*,*N*′-Propylenebis[nicotinamide].

Никаравен

$C_{15}H_{16}N_4O_2$ = 284.3.

CAS — 79455-30-4.



Profile

Nicaraven is under investigation as a cerebral vasodilator.

◊ References.

1. Jain KK. Nicaraven for the treatment of cerebral vasospasm in subarachnoid haemorrhage. *Expert Opin Invest Drugs* 2000; **9:** 859–70.

Nicergoline *(BAN, USAN, rINN)*

FI-6714; Nicergolin; Nicergolina; Nicergolinas; Nicergolinum; Nisergoliini; Nisergolin. 10α-Methoxy-1,6-dimethylergolin-8β-ylmethyl 5-bromonicotinate.

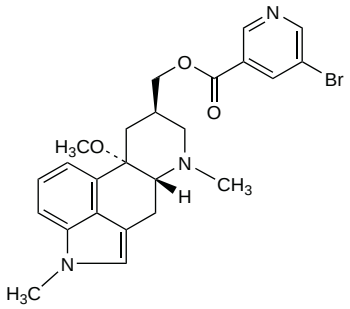
Ницерголин

$C_{24}H_{26}BrN_3O_3$ = 484.4.

CAS — 27848-84-6.

ATC — C04AE02.

ATC Vet — QC04AE02.



Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Nicergoline). A fine to granular white or yellowish powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane.

Adverse Effects and Precautions

Adverse effects that may occur after nicergoline include gastrointestinal disturbances and, particularly after parenteral doses, hypotension.

Incidence of adverse effects. Adverse effects occurred in 25 of 359 patients with cerebrovascular insufficiency treated with nicergoline for 1 month;[1] the drug had to be withdrawn in 11. The reactions included 6 cases of hot flushes, 8 of general malaise, 2 of agitation, 3 of hyperacidity, 1 of nausea, 3 of diarrhoea, and 2 of dizziness and somnolence.

1. Dauverchain J. Bedeutung von Nicergolin bei der symptomatischen Behandlung des arteriellen Hochdrucks und der chronischen, zerebro-vaskulären Insuffizienz. *Arzneimittelforschung* 1979; **29:** 1308–10.

Porphyria. Nicergoline is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems, although there is conflicting evidence of porphyrinogenicity.

Interactions

For a study indicating that nicergoline enhances the cardiac depressant action of propranolol, see Ergot Derivatives, in Interactions of Beta Blockers, p.1229.

Uses and Administration

Nicergoline is an ergot derivative. It has been used similarly to codergocrine mesilate (p.364) to treat symptoms of mental deterioration associated with cerebrovascular insufficiency (see Dementia, p.362) and has also been used in peripheral vascular disease (p.1178). Nicergoline has been given in doses of up to 60 mg daily by mouth in divided doses, and by intramuscular injection in doses of 2 to 4 mg twice daily; 4 to 8 mg daily has been given by intravenous infusion. Nicergoline tartrate has been used in parenteral dosage forms.

◊ References.

1. Ronchi F, *et al.* Symptomatic treatment of benign prostatic obstruction with nicergoline: a placebo controlled clinical study and urodynamic evaluation. *Urol Res* 1982; **10:** 131–4.
2. Bousquet J, *et al.* Double-blind, placebo-controlled study of nicergoline in the treatment of pruritus in patients receiving maintenance hemodialysis. *J Allergy Clin Immunol* 1989; **83:** 825–8.
3. Saletu B, *et al.* Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: a double-blind, placebo-controlled, clinical and EEG/ERP mapping study. *Psychopharmacology (Berl)* 1995; **117:** 385–95.
4. Herrmann WM, *et al.* A multicenter randomized double-blind study on the efficacy and safety of nicergoline in patients with multi-infarct dementia. *Dementia Geriatr Cogn Disord* 1997; **8:** 9–17.
5. Fioravanti M, Flicker L. Nicergoline for dementia and other age associated forms of cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 28/04/05).
6. Felisati G, *et al.* Nicergoline in the treatment of dizziness in elderly patients: a review. *Arch Gerontol Geriatr Suppl* 2004; 163–70.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cergodun; Nicergolent†; Sermion; ***Austria:*** Ergotop; Nicergin; Sermion; ***Braz.:*** Sermion; ***Chile:*** Sermion; ***Cz.:*** Ergotop; Nilogrin†; Sermion; ***Fr.:*** Sermion; ***Ger.:*** Circo-Maren†; Ergobel; Nicergobeta; Nicerium; Sermion†; ***Gr.:*** Albotyl†; Sermion; ***Hong Kong:*** Cergodun; Qualigoline; Sermion; ***Hung.:*** Ergotop; Sermion; ***Indon.:*** Serolin; ***Ital.:*** Cebran; Nicer†; Sermion; ***Jpn:*** Sermion; ***Mex.:*** Sermion; ***Philipp.:*** Sermion; ***Pol.:*** Adavin; Circulat; Nicerin; Nilogrin; Sermion; ***Port.:*** Erg XXI†; Sermion; ***Rus.:*** Nilogrin (Нилогрин); Sermion (Сермион); ***Spain:*** Fisifax†; Sermion; Varson; ***Switz.:*** Sermion; ***Thai.:*** Sermion; ***Turk.:*** Sermion; ***Venez.:*** Sermion.

Multi-ingredient: ***Arg.:*** Angiolit†; Sibelium Plus.

Nicotine

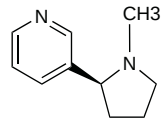
Nicotina; Nicotinum; Nikotiini; Nikotin; Nikotinas. (*S*)-3-(1-Methylpyrrolidin-2-yl)pyridine.

$C_{10}H_{14}N_2$ = 162.2.

CAS — 54-11-5.

ATC — N07BA01.

ATC Vet — QN07BA01; QP53AX13.



Description. Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, *Nicotiana tabacum* and related species (Solanaceae). Tobacco leaves contain 0.5 to 8% of nicotine combined as malate or citrate.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Nicotine). A colourless or brownish, volatile, hygroscopic, viscous liquid. Soluble in water; miscible with dehydrated alcohol. Store under nitrogen in airtight containers. Protect from light.

USP 31 (Nicotine). It should be stored under nitrogen at a temperature below 25°. Protect from light and moisture.

Nicotine Polacrilex *(USAN)*

CAS — 96055-45-7.

ATC — N07BA01.

ATC Vet — QN07BA01.

Pharmacopoeias. In *US.*

USP 31 (Nicotine Polacrilex). A weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene, in complex with nicotine. Store in airtight containers.

Nicotine Resinate

Nicotine, résinate de; Nicotini resinas; Nicotinresinat; Nikotiiniresinaatti; Nikotino rezinatas; Nikotin-resinát; Nikotin-rezinát.

ATC — N07BA01.

ATC Vet — QN07BA01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Nicotine Resinate). A complex of nicotine with a weak cationic exchange resin. It may contain glycerol. A white or slightly yellowish powder. Practically insoluble in water. Store in airtight containers. Protect from light.

Nicotine Tartrate

Nicotine Bitartrate *(USAN).*

$C_{10}H_{14}N_2,2C_4H_6O_6,2H_2O$ = 498.4.

CAS — 65-31-6 (anhydrous nicotine tartrate).

ATC — N07BA01.

ATC Vet — QN07BA01.

Dependence and Withdrawal

Nicotine dependence is most commonly associated with cigarette smoking. It is characterised by a strong desire to continue taking the agent, a physical and psychological need for it, and a characteristic abstinence syndrome on withdrawal. Common symptoms seen on nicotine withdrawal include irritability, anxiety, depression, restlessness, poor concentration, increased appetite, weight gain, and insomnia. The management of smoking cessation is discussed under Uses and Administration, below.

Mild withdrawal symptoms have been reported from nicotine replacement preparations used to aid smoking cessation.

◊ References.

1. Hatsukami D, *et al.* Physical dependence on nicotine gum: effect of duration of use. *Psychopharmacology (Berl)* 1993; **111:** 449–56.
2. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction: the implications for tobacco regulation. *N Engl J Med* 1994; **331:** 123–5.
3. Keenan RM, *et al.* Pharmacodynamic effects of cotinine in abstinent cigarette smokers. *Clin Pharmacol Ther* 1994; **55:** 581–90.
4. Slade J, *et al.* Nicotine and addiction: the Brown and Williamson documents. *JAMA* 1995; **274:** 225–33.
5. Kessler DA. Nicotine addiction in young people. *N Engl J Med* 1995; **333:** 186–9.
6. Doll R, Crofton J, eds. Tobacco and health. *Br Med Bull* 1996; **52:** 1–223.
7. Benowitz NL. Nicotine addiction. *Prim Care* 1999; **26:** 611–31.
8. Colby SM, *et al.* Are adolescent smokers dependent on nicotine? A review of the evidence. *Drug Alcohol Depend* 2000; **59** (suppl 1): S83–S95.
9. Royal College of Physicians. *Nicotine addiction in Britain: a report of the Tobacco Advisory Group of the Royal College of Physicians.* London: Royal College of Physicians, 2000. Also available at: http://www.rcplondon.ac.uk/pubs/books/nicotine/index.htm (accessed 30/07/08)
10. West R, *et al.* A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology (Berl)* 2000; **149:** 198–202.

Adverse Effects and Treatment

Nicotine is a highly toxic substance and in acute poisoning death may occur within 1 hour due to respiratory failure arising from paralysis of the muscles of respiration. The fatal oral dose of nicotine for an adult is from 40 to 60 mg.

Less severe poisoning causes initial stimulation followed by depression of the autonomic nervous system. Typical symptoms include burning of the mouth and throat, nausea and salivation, abdominal pain, vomiting, diarrhoea, dizziness, weakness, hypertension followed by hypotension, mental confusion, headache, hearing and visual disturbances, dyspnoea, faintness, convulsions, sweating, and prostration. Transient cardiac standstill or paroxysmal atrial fibrillation may occur.

Nicotine is rapidly absorbed through the skin or by inhalation as well as by ingestion, and nicotine poisoning may occur due to careless handling when it is used as a horticultural insecticide.

Prompt treatment of nicotine poisoning is essential. If contact was with the skin, contaminated clothing should be removed and the skin washed thoroughly with cold water without rubbing. If the patient has swallowed nicotine, gastric lavage and activated charcoal may be beneficial. Treatment is supportive and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation.

Apart from effects such as dizziness, headache, and gastrointestinal disturbances mentioned above, adverse effects associated with *nicotine replacement preparations* have also included cold and flu-like symptoms, palpitations, insomnia, vivid dreams, myalgia, chest pain, blood pressure changes, anxiety, irritability, somnolence, and dysmenorrhoea. Allergic reactions have been reported. Adverse effects associated with specific preparations include skin reactions with transdermal patches; nasal irritation, epistaxis, lachrymation, and sensations in the ear with the nasal spray; throat irritation with the spray, inhalator, sublingual tablets, lozenges, or chewing gum; aphthous ulceration with the inhalator, sublingual tablets, lozenges, or chewing gum; increased salivation and sometimes swelling of the tongue with chewing gum; cough, rhinitis, stomatitis, sinusitis, and dry mouth with the inhalator; and unpleasant taste with the sublingual tablets or lozenges. Excessive swallowing of nicotine released from oral replacement preparations may cause hiccups in the first few days of treatment.

◊ References.

1. Greenland S, *et al.* A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety* 1998; **18:** 297–308.
2. Gourlay SG, *et al.* Predictors and timing of adverse experiences during transdermal nicotine therapy. *Drug Safety* 1999; **20:** 545–55.

Adverse effects of tobacco products. Chronic use of tobacco is linked to a variety of diseases. By the mid-1960s, epidemiological data established tobacco smoking as a cause of lung cancer (p.668). Smoking is also associated with cancers of the larynx, mouth, cervix, bladder, pancreas, oesophagus, stomach, and kidneys, and with leukaemia.[1] Smoking is a risk factor in cardiovascular, respiratory, and peripheral and cerebral vascular diseases.[1-3] Smoking also increases the risk of developing peptic ulcer disease and may affect other gastrointestinal disorders.[2] There is also evidence that smoking tobacco products increases the risk of developing age-related macular degeneration,[4] type 2 diabetes mellitus,[5] and adenomatous polyps.[6]

Maternal smoking in pregnancy is associated with low birthweight infants and increased risk of abortion, still-birth, and neonatal death (see also Pregnancy under Precautions, below).

Passive smoking refers to inhalation of secondhand tobacco smoke or environmental tobacco smoke. Risks to health from passive exposure are lower than those from active smoking. However, studies have established passive smoking as a cause of lung cancer;[7] passive smoking is also associated with increased risk of heart disease[8] and chronic respiratory disease.[9,10] Smokeless tobacco products also carry risks to health, for example the association of cancers of the head and neck (see p.666) with the use of mixtures of tobacco and areca (p.2259) and probably snuff or chewing tobacco.[11,12]

1. Wald NJ, Hackshaw AK. Cigarette smoking: an epidemiological overview. *Br Med Bull* 1996; **52:** 3–11.
2. Ashton H. Adverse effects of nicotine. *Adverse Drug React Bull* 1991; **149**: 560–3.
3. Teo KK, *et al.* INTERHEART Study Investigators. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006; **368:** 647–58.
4. Tan JSL, *et al.* Smoking and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Arch Ophthalmol* 2007; **125:** 1089–95.
5. Willi C, *et al.* Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2007; **298:** 2654–64.
6. Botteri E, *et al.* Cigarette smoking and adenomatous polyps: a meta-analysis. *Gastroenterology* 2008; **134:** 388–95.
7. Lam TH. Passive smoking in perspective. *Med Toxicol Adverse Drug Exp* 1989; **4:** 153–62.