Gastrointestinal drugs. The antidiarrhoeal *loperamide* markedly reduced exposure to saquinavir in 12 healthy subjects given a single dose of both drugs.[1] Exposure was reduced by about 54%, a reduction of the same order of magnitude as seen with enzyme inducers such as rifampicin, although the mechanism in this case was thought likely to be impaired absorption of the antiviral. Prolonged use of loperamide might lead to substantial reductions in saquinavir plasma concentrations, and reduced clinical efficacy. Plasma concentrations of loperamide were also increased, and those of its metabolite desmethylloperamide correspondingly reduced, but this was thought unlikely to be of clinical significance.

Atazanavir and indinavir depend on acid pH in the stomach for adequate absorption, and acid-suppressive therapies such as *histamine H_2-antagonists* and *proton pump inhibitors* may significantly reduce their absorption; if acid-suppressive therapy is necessary, these HIV-protease inhibitors should be boosted with low-dose ritonavir to ensure adequate antiretroviral activity.[2]

For the effect of HIV-protease inhibitors on *cisapride*, see p.1721.

1. Mikus G, *et al.* Reduction of saquinavir exposure by coadministration of loperamide: a two-way pharmacokinetic interaction. *Clin Pharmacokinet* 2004; **43:** 1015–24.
2. Fulco PP, *et al.* Acid suppressive therapy and the effects on protease inhibitors. *Ann Pharmacother* 2006; **40:** 1974–83.

Grapefruit. Exposure to saquinavir was increased by 50% when taken with grapefruit juice;[1] however, licensed product information does not recommend any adjustment of dosage of saquinavir.

1. Kupferschmidt HHT, *et al.* Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in men. *Br J Clin Pharmacol* 1998; **45:** 355–9.

Hormonal contraceptives. For the effect of HIV-protease inhibitors on hormonal contraceptives, see p.2068.

Interleukin-2. Plasma concentrations of indinavir were increased[1] during use with interleukin-2.

1. Piscitelli SC, *et al.* Alteration in indinavir clearance during interleukin-2 infusions in patients infected with the human immunodeficiency virus. *Pharmacotherapy* 1998; **18:** 1212–16.

Paclitaxel. For the effect of HIV-protease inhibitors on paclitaxel, see Interactions, Antivirals, p.759.

Phenylpropanolamine. For a possible interaction between phenylpropanolamine and antiretrovirals including indinavir, see Stavudine, p.907.

Sildenafil. For the effect of HIV-protease inhibitors on sildenafil, including a report of fatal myocardial infarction after sildenafil in a patient receiving ritonavir and saquinavir, see p.2194.

Statins. HIV-protease inhibitors may inhibit the metabolism of statins metabolised by CYP3A4 isoenzymes resulting in an increased risk of myopathy. Although those statins less dependent on CYP3A4 for metabolism may be used in certain circumstances to manage HIV-protease inhibitor-induced lipid disorders, use with lovastatin or simvastatin should be avoided, and HIV-protease inhibitors should be given with caution in patients receiving atorvastatin or rosuvastatin.

Tacrolimus. HIV-protease inhibitors may inhibit the metabolism of tacrolimus (see Antivirals, p.1845).

Theophylline. For a potential effect of ritonavir on theophylline, see p.1144.

Warfarin. For the effect of HIV-protease inhibitors on warfarin, see p.1430.

Antiviral Action

Indinavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 proteases with a tenfold greater selectivity for HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Indinavir is rapidly absorbed after oral doses producing peak plasma concentrations in 0.8 hours (range 0.5 to 1.1 hours). Bioavailability is about 65% after a single 800-mg dose. Absorption is reduced if given with a meal high in calories, fat, and protein but is less affected by a light meal (for the effect of pH see Gastrointestinal Drugs under Interactions, above). At doses up to 1 g, increases in plasma concentration are proportionately greater than increases in dose. Plasma protein binding is about 60%. Indinavir is reported to cross the blood-brain barrier. It undergoes oxidative metabolism by cytochrome P450 isoenzyme CYP3A4 and glucuronidation. At least seven metabolites (1 glucuronide and 6 oxidative metabolites) have been identified. The elimination half-life is 1.8 hours. Less than 20% of the absorbed dose is excreted in the urine, about half of this as unchanged drug. The remainder is excreted in the faeces.

◊ References.

1. Ståhle L, *et al.* Indinavir in cerebrospinal fluid of HIV-1-infected patients. *Lancet* 1997; **350:** 1823.
2. Bernard L, *et al.* Indinavir concentrations in hair from patients receiving highly active antiretroviral therapy. *Lancet* 1998; **352:** 1757–8.
3. Wintergerst U, *et al.* Use of saliva specimens for monitoring indinavir therapy in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2000; **44:** 2572–4.
4. Haas DW, *et al.* Steady-state pharmacokinetics of indinavir in cerebrospinal fluid and plasma among adults with human immunodeficiency virus type 1 infection. *Clin Pharmacol Ther* 2000; **68:** 367–74.
5. Burger DM, *et al.* Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 2001; **45:** 701–5.
6. Kappelhoff BS, *et al.* Population pharmacokinetics of indinavir alone and in combination with ritonavir in HIV-1-infected patients. *Br J Clin Pharmacol* 2005; **60:** 276–86.
7. Unadkat JD, *et al.* Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2007; **51:** 783–6.

Uses and Administration

Indinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when indinavir is used alone, and it is therefore used with other antiretrovirals.

Indinavir is given orally as the sulfate, but doses are expressed in terms of the base; 116 mg of indinavir sulfate is equivalent to about 100 mg of indinavir. It is given in a usual adult dose of 800 mg every 8 hours. For the *reduced* doses recommended in patients taking azole antifungals or the NNRTI delavirdine, and *increased* doses in those also taking rifabutin or nevirapine, see Antibacterials, Antifungals, and Antivirals, under Interactions, above. Indinavir should be given either 1 hour before or 2 hours after meals, or with a light, low-fat meal. Adequate hydration should be maintained. Treatment may have to be interrupted if acute episodes of nephrolithiasis occur.

For details of doses in children and adolescents, see below. For details of modified dosage to be used in patients with hepatic impairment, see below.

Administration in children. For the treatment of HIV infection in children 4 years of age and older indinavir is given orally with other antiretroviral drugs. A dose of 500 mg/m^2 every 8 hours is recommended; doses should not exceed the adult dose (see above).

Administration in hepatic impairment. A reduction in the oral dose of indinavir to 600 mg every 8 hours is recommended for patients with mild to moderate hepatic insufficiency due to cirrhosis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avural; Crixivan; Elvenavir; Forli; Indilea; Inhibisam; ***Austral.:*** Crixivan; ***Austria:*** Crixivan; ***Belg.:*** Crixivan; ***Braz.:*** Crixivan; Dinavir†; Indinax; ***Canad.:*** Crixivan; ***Chile:*** Crixivan; ***Cz.:*** Crixivan; ***Denm.:*** Crixivan; ***Fin.:*** Crixivan; ***Fr.:*** Crixivan; ***Ger.:*** Crixivan; ***Gr.:*** Crixivan; ***Hong Kong:*** Crixivan; ***Hung.:*** Crixivan; ***India:*** Indivan; ***Irl.:*** Crixivan; ***Israel:*** Crixivan; ***Ital.:*** Crixivan; ***Jpn:*** Crixivan; ***Malaysia:*** Crixivan; ***Mex.:*** Crixivan; Indilan; ***Neth.:*** Crixivan; ***Norw.:*** Crixivan; ***NZ:*** Crixivan; ***Philipp.:*** Crixivan; ***Pol.:*** Crixivan; ***Port.:*** Crixivan; ***Rus.:*** Crixivan (Криксиван); ***S.Afr.:*** Crixivan; ***Singapore:*** Crixivan; ***Spain:*** Crixivan; ***Swed.:*** Crixivan; ***Switz.:*** Crixivan; ***Thai.:*** Crixivan; ***Turk.:*** Crixivan; ***UK:*** Crixivan; ***USA:*** Crixivan; ***Venez.:*** Crixivan; Indivan.

Inosine Pranobex *(BAN)*

Inosine Dimepranol Acedoben *(pINNM)*; Inosin Pranobeks; Inosina Dimepranol Acedobén; Inosine Acédobène Diméprano; Inosinum Dimepranolum Acedobenum; Inosinum pranobexum; Inosiplex; Isoprinosine; Methisoprinol; NP-113; NPT-10381. Inosine 2-hydroxypropyldimethylammonium 4-acetamidobenzoate (1:3).

Инозин Димепранол Ацедобен

$C_{10}H_{12}N_4O_5$:$C_{14}H_{22}N_2O_4$ (1:3) = 1115.2.

CAS — 36703-88-5.

ATC — J05AX05.

ATC Vet — QJ05AX05.

NOTE. Dimepranol Acedoben is *pINN* and *USAN*.

Adverse Effects and Precautions

Some patients have had transient nausea, vomiting, headaches, arthralgia, fatigue, vertigo, raised liver enzymes, pruritus, and skin rashes. Metabolism of the inosine content of inosine pranobex leads to increased serum and urine concentrations of uric acid; caution is therefore recommended in treating patients with renal impairment, gout, or hyperuricaemia.

Antiviral Action

Inosine pranobex appears to owe its activity in viral infections more to its capacity to modify or stimulate cell-mediated immune processes than to a direct action on the virus.

Pharmacokinetics

Inosine pranobex is reported to be rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 hour after an oral dose. It is also rapidly metabolised with a plasma half-life of 50 minutes, the inosine portion of the complex yielding uric acid; the other components undergo oxidation and glucuronidation. The metabolites are excreted in the urine.

◊ References.

1. Nielsen P, Beckett AH. The metabolism and excretion in man of NN-dimethylamino-isopropanol and p-acetamido-benzoic acid after administration of isoprinosine. *J Pharm Pharmacol* 1981; **33:** 549–50.

Uses and Administration

Inosine pranobex is a complex of inosine (p.2325) with dimepranol acedoben ((±)-1-(dimethylamino)-2-propanol *p*-acetamidobenzoate). It has been used in the treatment of various viral infections (see below), including herpes simplex, genital warts, and subacute sclerosing panencephalitis, although other treatments or measures are preferred. The oral dose in mucocutaneous herpes simplex is 1 g four times daily for 7 to 14 days. An oral dose of 1 g three times daily is given for 14 to 28 days as an adjunct to standard topical treatment for genital warts. In subacute sclerosing panencephalitis, the oral dose is 50 to 100 mg/kg daily in divided doses given every 4 hours.

◊ Reviews.

1. Campoli-Richards DM, *et al.* Inosine pranobex: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1986; **32:** 383–424.

Alopecia. Oral inosine pranobex (50 mg/kg daily in 5 divided doses for 12 weeks) has been investigated[1] with some apparent benefit in the treatment of recalcitrant alopecia areata (p.1577).

1. Georgala S, *et al.* Inosiplex for treatment of alopecia areata: a randomized placebo-controlled study. *Acta Derm Venereol* 2006; **86:** 422–4.

Subacute sclerosing panencephalitis. Inosine pranobex has been tried[1,2] in the treatment of subacute sclerosing panencephalitis, a complication of measles (p.860), but the results of clinical studies have been equivocal. Some success has been reported when inosine pranobex has been given with interferons and other antivirals. However, a randomised study involving 121 patients, of whom 67 completed analysis, was unable to show any difference between an oral regimen of inosine pranobex 100 mg/kg daily in 3 divided doses (up to a maximum of 3 g daily) for 6 months, and the same dose combined with intraventricular interferon alfa, although the outcomes, which were considered satisfactory in about 35% of cases, were better than the 10% remission rate in historical controls, implying some benefit with either treatment.[3]

1. Haddad FS, Risk WS. Isoprinosine treatment in 18 patients with subacute sclerosing panencephalitis: a controlled study. *Ann Neurol* 1980; **7:** 185–8.
2. Jones CE, *et al.* Inosiplex therapy in subacute sclerosing panencephalitis: a multicentre, non-randomised study in 98 patients. *Lancet* 1982; **i:** 1034–7.
3. Gascon GG. International Consortium on Subacute Sclerosing Panencephalitis. Randomized treatment study of inosiplex versus combined inosiplex and intraventricular interferon-α in subacute sclerosing panencephalitis (SSPE): international multicenter study. *J Child Neurol* 2003; **18:** 819–27. Correction. *ibid.* 2004; **19:** 342.

Warts. Although of no apparent benefit in the treatment of palmar/plantar warts,[1] oral inosine pranobex has been shown to be of value in the treatment of refractory genital warts (p.1584) in the cervix,[2] as well as producing some apparent epithelial morphological improvement in women with subclinical human papillomavirus infection of the vulva.[3]

1. Berth-Jones J, Hutchinson PE. Modern treatment of warts: cure rates at 3 and 6 months. *Br J Dermatol* 1992; **127:** 262–5.
2. Georgala S, *et al.* Oral inosiplex in the treatment of cervical condylomata acuminata: a randomised placebo-controlled trial. *BJOG* 2006; **113:** 1088–91.
3. Tay SK. Efficacy of inosine pranobex oral therapy in subclinical human papillomavirus infection of the vulva: a randomized double-blinded placebo controlled study. *Int J STD AIDS* 1996; **7:** 276–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Isoprinosin; ***Belg.:*** Isoprinosine; ***Canad.:*** Imunovir; ***Chile:*** Isoprinosine; ***Cz.:*** Isoprinosine; ***Fr.:*** Isoprinosine; ***Ger.:*** delimmun; Isoprinosine; ***Gr.:*** Isoprinosine; ***Hong Kong:*** Qualiprinol; ***Hung.:*** Isoprinosine; ***Indon.:*** Isprinol; ***Irl.:*** Imunovir; Isoprinosine; ***Ital.:*** Avirin†; Farviran†; Virustop†; Viruxan; ***Mex.:*** Isoprinosine; Pranosine; ***NZ:*** Imunovir; ***Philipp.:*** Immunosin; Isoprinosine; ***Pol.:*** Groprinosin; ***Port.:*** Isovir; ***Rus.:*** Isoprinosine (Изопринозин); ***Singapore:*** Imin; ***UK:*** Imunovir.

Interferon Alfa *(BAN, rINN)*

IFN-α; Interferón-α; Interferon-α; Interferón alfa; Interféron alfa; Interferon alpha; Interferoni alfa; Interferonialfa; Interferonum Alfa; Ro-22-8181 (interferon alfa-2a); Sch-30500 (interferon alfa-2b).

Интерферон Альфа

CAS — 74899-72-2 (interferon alfa); 76543-88-9 (interferon alfa-2a); 99210-65-8 (interferon alfa-2b); 118390-30-0 (interferon alfacon-1); 198153-51-4 (peginterferon alfa-2a); 215647-85-1 (peginterferon alfa-2b).

ATC — L03AB01 (natural); L03AB04 (2a); L03AB05 (2b); L03AB06 (n1); L03AB09 (alfacon-1); L03AB10 (peginterferon alfa-2b); L03AB11 (peginterferon alfa-2a).

ATC Vet — QL03AB01 (natural); QL03AB04 (2a); QL03AB05 (2b); QL03AB06 (n1); QL03AB09 (alfacon-1); QL03AB10 (peginterferon alfa-2b); QL03AB11 (peginterferon alfa-2a).

NOTE. Interferon alfa was previously known as leucocyte interferon or lymphoblastoid interferon.

Interferon alfa-2a, alfa-2b, alfa-n1, and alfa-n3 are *USAN*.

Interferon alfacon-1 (*BAN*, *USAN*, *rINN*) is a recombinant nonnaturally occurring alfa interferon. Peginterferon alfa-2a (*BAN*, *USAN*, *rINN*) and peginterferon alfa-2b (*BAN*, *rINN*) are interferons pegylated by conjugation with macrogols.

Pharmacopoeias. *Chin.* includes monographs for recombinant human alfa-2a and alfa-2b. *Eur.* (see p.vii) includes Interferon Alfa-2 Concentrated Solution.

Ph. Eur. 6.2 (Interferon Alfa-2 Concentrated Solution; Interferoni Alfa-2 Solutio Concentrata). It is produced by a method based on recombinant DNA technology using bacteria as host cells. It is a clear, colourless or slightly yellowish liquid. Store in airtight containers at a temperature of –20° or below. Protect from light.

Nomenclature. Interferon alfa may be derived from leucocytes or lymphoblasts, or produced by recombinant DNA technology. Sub-species of the human alfa gene may produce interferon alfa with protein variants or a mixture of proteins. The protein variants may be designated by a number (as in interferon alfa-2) which may be further qualified by a letter to indicate the amino-acid sequences at positions 23 and 34:

- interferon alfa-2a has lysine at 23 and histidine at 34
- interferon alfa-2b has arginine at 23 and histidine at 34
- interferon alfa-2c has arginine at both positions

In the case of a mixture of proteins an alphanumeric designation is given (as in interferon alfa-n1). Interferon alfacon-1 varies from interferon alfa-2 in 20 of 166 amino acids.

The name may be further elaborated on the label by approved sets of initials in parentheses to indicate the method of production: (rbe) indicates production from bacteria (*Escherichia coli*) genetically modified by recombinant DNA technology; (lns) indicates production from cultured lymphoblasts from the Namalwa cell line that have been stimulated by a Sendai virus; (bls) indicates production from leucocytes from human blood that have been stimulated by a Sendai virus.

References.

1. Finter NB. The naming of cats—and alpha-interferons. *Lancet* 1996; **348:** 348–9.

Adverse Effects and Treatment

The adverse effects of interferon are varied and the natural products appear to be less toxic than the pure synthetic compounds. The frequency and severity of adverse effects of peginterferon alfa appear to be similar to those for interferon alfa although dose-related neutropenia and thrombocytopenia and injection site reactions are more common. Clinical experience suggests that interferons beta and gamma have similar adverse effects.

Adverse effects are generally mild and reversible at doses less than 5 million international units/day. The majority of patients on interferon treatment have 'flu-like' symptoms such as loss of appetite, fever, chills, fatigue, headache, malaise, myalgia, arthralgia, and sweating. These symptoms tend to be dose-related, are most likely to occur at the start of treatment, and mostly respond to paracetamol (but for a possible interaction with paracetamol, see Interactions, below).

Other common adverse effects are alopecia, asthenia, weight loss, anxiety, depression, dermatitis, diarrhoea, irritability, nausea, nervousness, neutropenia, pruritus, sleep disturbances, taste alteration, and vomiting. Serious adverse effects reported include neuropsychiatric disorders (homicidal ideation, suicidal ideation, suicide attempt, and suicide) and neurological disturbances (confusion, coma, and seizures), severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and rarely, aplastic anaemia), cardiovascular disorders (hypo- or hypertension, supraventricular arrhythmias and myocardial infarction), endocrine disorders (such as thyroid disorders and diabetes mellitus), pulmonary disorders (dyspnoea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic or ischaemic colitis), pancreatitis, and ophthalmologic disorders (such as decrease or loss of vision, retinopathy including macular oedema and retinal thrombosis or haemorrhages, optic neuritis and papilloedema).

Hypersensitivity reactions, including anaphylaxis, have occurred, and interferon therapy may cause or exacerbate auto-immune disorders (such as idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, psoriasis, SLE, rheumatoid arthritis, and interstitial nephritis).

Hypertriglyceridaemia, sometimes severe, has been seen. High doses may cause electrolyte disturbances including decreased calcium concentrations. There may be signs of altered liver function and hepatitis has been reported. Renal failure and nephrotic syndrome have also occurred. Interferons may impair fertility and menstrual irregularities have been reported, particularly with interferon beta. Subcutaneous injection may produce a reaction at the injection site, predominantly mild inflammation or erythema, but pain, hypersensitivity, and other non-specific reactions have been reported. The reaction is reported frequently with interferon beta, which can produce severe reactions including local necrosis.

Adverse effects of peginterferon alfa (alone or with ribavirin) reported in patients co-infected with hepatitis C virus and HIV, are similar to those reported in patients infected only with hepatitis C virus. Although haematological adverse effects such as neutropenia, thrombocytopenia, and anaemia occurred more often in co-infected patients, most patients could be managed by dose adjustments. Other adverse effects reported in co-infected patients given peginterferon and ribavirin include apathy, raised blood amylase, chapped lips, chromaturia, raised gamma-glutamyltransferase and hepatitis, influenza, lactic acidosis (including hyperlactacidaemia), lipodystrophy, mood alteration, pain in the pharynx, larynx, back, and limbs, pneumonia, and tinnitus. Peginterferon treatment was associated with decreases in CD4+ cell counts within the first 4 weeks that were reversible when the dose was reduced or stopped; no negative impact was noted on the control of HIV viraemia during treatment or follow-up.

Nasal dosage may produce mucosal irritation and damage.

◊ Reviews.

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Pardo M, *et al.* Risks and benefits of interferon-α in the treatment of hepatitis. *Drug Safety* 1995; **13:** 304–16.
3. Kirkwood JM, *et al.* Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. *J Clin Oncol* 2002; **20:** 3703–18.
4. Sleijfer S, *et al.* Side effects of interferon-alpha therapy. *Pharm World Sci* 2005; **27:** 423–31.

Effects on the blood. Interferon alfa has myelosuppressive effects and the commonest haematological adverse effects associated with its use are dose-related leucopenia, neutropenia, and thrombocytopenia; anaemia is rarely reported. Other reported effects associated with interferon alfa include immune haemolytic anaemia[1] and immune thrombocytopenia.[2,3] Haemorrhage occurred in a patient with immune thrombocytopenic purpura treated with interferon alfa,[4] and it was thought prudent to use interferons with caution, if at all, in this condition.[3,4] Reports of clotting disorders are rare; bleeding associated with induction of factor VIII inhibitor has been seen in a patient given interferon alfa to enhance hydroxycarbamide therapy for chronic myeloid leukaemia.[5] Thrombosis associated with interferon alfa has also been reported.[6]

Restoration of bone-marrow function after marrow transplantation was delayed in 3 patients given a human interferon alfa preparation.[7] Laboratory results showed an inhibition of granulocyte colony growth by human leucocyte interferon alfa. It was considered that interferon alfa was contra-indicated in patients with severe bone-marrow insufficiency and should not be given to marrow transplant patients before the graft was fully functional. However, in another 5 patients recombinant interferon alfa did not affect bone marrow transplants, although 3 patients experienced fever and chills, 4 had more than a 60% reduction in absolute peripheral granulocyte counts, and 4 had a 37 to 80% reduction in absolute platelet counts.[8] Lymphocytes were increased in all patients; blood counts returned to normal when interferon therapy stopped. Interferon alfa produced a decline in CD4+ T-lymphocytes resulting in opportunistic infections in 2 HIV-positive patients being treated for chronic hepatitis C.[9]

1. Akard LP, *et al.* Alpha-interferon and immune hemolytic anemia. *Ann Intern Med* 1986; **105:** 306.
2. McLaughlin P, *et al.* Immune thrombocytopenia following α-interferon therapy in patients with cancer. *JAMA* 1985; **254:** 1353–4.
3. Färkkilä M, Iivanainen M. Thrombocytopenia and interferon. *BMJ* 1988; **296:** 642.
4. Matthey F, *et al.* Bleeding in immune thrombocytopenic purpura after alpha-interferon. *Lancet* 1990; **335:** 471–2.
5. English KE, *et al.* Acquired factor VIII inhibitor in a patient with chronic myelogenous leukaemia receiving interferon-alfa therapy. *Ann Pharmacother* 2000; **34:** 737–9.
6. Durand JM, *et al.* Thrombosis and recombinant interferon-α. *Am J Med* 1993; **95:** 115.
7. Nissen C, *et al.* Toxicity of human leucocyte interferon preparations in human bone-marrow cultures. *Lancet* 1977; **i:** 203–4.
8. Winston DJ, *et al.* Safety and tolerance of recombinant leukocyte A interferon in bone marrow transplant recipients. *Antimicrob Agents Chemother* 1983; **23:** 846–51.
9. Pesce A, *et al.* Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1 infected patients. *Lancet* 1993; **341:** 1597.

Effects on the cardiovascular system. Hypotension or hypertension, tachycardia, and distal cyanosis are the most commonly reported cardiovascular adverse effects. Other reported cardiac complications include cardiac arrhythmias, atrioventricular block, symptoms of ischaemic heart disease, including myocardial infarction and sudden death, congestive heart failure, acute dyspnoea, pericardial effusion,[1,2] and cardiomyopathy.[1,3,4] Cardiac toxicity was not related to the daily or cumulative total dose, or duration of treatment and is usually reversible on stopping interferon treatment.[1]

Peripheral vascular complications such as Raynaud's syndrome[5-9] have been associated with interferon alfa therapy and other types of interferon.

1. Sonnenblick M, Rosin A. Cardiotoxicity of interferon. A review of 44 cases. *Chest* 1991; **99:** 557–61.
2. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
3. Angulo MP, *et al.* Reversible cardiomyopathy secondary to α-interferon in an infant. *Pediatr Cardiol* 1999; **20:** 293–4.
4. Kuwata A, *et al.* A case of reversible dilated cardiomyopathy after α-interferon therapy in a patient with renal cell carcinoma. *Am J Med Sci* 2002; **324:** 331–4.
5. Bachmeyer C, *et al.* Raynaud's phenomenon and digital necrosis induced by interferon-alpha. *Br J Dermatol* 1996; **135:** 481–3.
6. Linden D. Severe Raynaud's phenomenon associated with interferon-β treatment for multiple sclerosis. *Lancet* 1998; **352:** 878–9.
7. Kruit WH, *et al.* Interferon-α induced Raynaud's syndrome. *Ann Oncol* 2000; **11:** 1501–2.
8. Schapira D, *et al.* Interferon-induced Raynaud's syndrome. *Semin Arthritis Rheum* 2002; **32:** 157–62.
9. Iorio R, *et al.* Severe Raynaud's phenomenon with chronic hepatitis C disease treated with interferon. *Pediatr Infect Dis J* 2003; **22:** 195–7.

Effects on the endocrine system. Both hypothyroidism[1,2] and hyperthyroidism[2,3] have been associated with interferon alfa therapy. Thyroid disorders are usually minor and regress on stopping the interferon (with or without other specific treatment). However a case of long-lasting ophthalmopathy as a result of interferon alfa-induced Graves' disease has been reported in a patient being treated for hepatitis C.[4]

The development of type 1 diabetes has also been associated with interferon alfa therapy,[5-8] and exacerbation of existing type 2 diabetes has been reported.[9,10] Reversible hypopituitarism has been reported in patients receiving interferon alfa.[11,12] Recombinant interferon gamma was reported not to affect thyroid function.[13]

1. Fentiman IS, *et al.* Primary hypothyroidism associated with interferon therapy of breast cancer. *Lancet* 1985; **i:** 1166.
2. Burman P, *et al.* Autoimmune thyroid disease in interferon-treated patients. *Lancet* 1985; **ii:** 100–1.
3. Schultz M, *et al.* Induction of hyperthyroidism by interferon-α-2b. *Lancet* 1989; **i:** 1452.
4. Binaghi M, *et al.* Ophtalmopathie de Basedow sévère liée à l'interféron alpha. *J Fr Ophtalmol* 2002; **25:** 412–15.
5. Fabris P, *et al.* Development of type 1 diabetes mellitus during interferon alfa therapy for chronic HCV hepatitis. *Lancet* 1992; **340:** 548.
6. Guerci A-P, *et al.* Onset of insulin-dependent diabetes mellitus after interferon-alfa therapy for hairy cell leukaemia. *Lancet* 1994; **343:** 1167–8.
7. Gori A, *et al.* Reversible diabetes in patient with AIDS-related Kaposi's sarcoma treated with interferon α-2a. *Lancet* 1995; **345:** 1438–9.
8. Murakami M, *et al.* Diabetes mellitus and interferon-α therapy. *Ann Intern Med* 1995; **123:** 318.
9. Campbell S, *et al.* Rapidly reversible increase in insulin requirement with interferon. *BMJ* 1996; **313:** 92.
10. Lopes EPA, *et al.* Exacerbation of type 2 diabetes mellitus during interferon-alfa therapy for chronic hepatitis B. *Lancet* 1994; **343:** 244. Correction. *ibid.*: 680.
11. Sakane N, *et al.* Reversible hypopituitarism after interferon-alfa therapy. *Lancet* 1995; **345:** 1305.