3. Piarroux R, *et al.* Are live saccharomyces yeasts harmful to patients? *Lancet* 1999; **353:** 1851–2.
4. Land MH, *et al.* Lactobacillus sepsis associated with probiotic therapy. *Pediatrics* 2005; **115:** 178–81.
5. Boyle RJ, *et al.* Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006; **83:** 1256–64.
6. Hammerman C, *et al.* Safety of probiotics: comparison of two popular strains. *BMJ* 2006; **333:** 1006–8.

Composition and viability. Some preparations of probiotics have been found to contain smaller quantities or different species of organisms to those specified on the label.[1] An FAO/WHO working group[2] published some guidelines that should be followed in order to claim that a food has a probiotic effect. These include the genus, species, and strain of the organisms in the preparation to be stated on the product label using currently recognised systematic nomenclature, and a statement of the minimum number of viable organisms remaining at the end of the product shelf-life.

1. Hamilton-Miller JMT, *et al.* "Probiotic" remedies are not what they seem. *BMJ* 1996; **312:** 55–6.
2. FAO/WHO. *Guidelines for the evaluation of probiotics in food.* London Ontario, Canada: Food and Agriculture Organization of the United Nations, 2002. Also available at: http:// www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf (accessed 11/02/08)

Uses. ***ALLERGIC DISORDERS.*** Oral ingestion of probiotic bacteria may play a role in the development of the adaptive immune system[1] and there has been some interest in their use in the management of allergic disorders such as atopic eczema.[2-5] However, reviews[6,7] of studies in allergic disorders have concluded that although there appears to be a reasonable theoretical basis for expecting benefit with probiotics, there are insufficient data to support their inclusion in routine treatment regimens for atopic eczema, perennial allergic rhinitis, or asthma.

1. Rinne M, *et al.* Effect of probiotics and breastfeeding on the *Bifidobacterium* and *Lactobacillus/Enterococcus* microbiota and humoral immune responses. *J Pediatr* 2005; **147:** 186–91.
2. Kalliomäki M, *et al.* Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003; **361:** 1869–71.
3. Rosenfeldt V, *et al.* Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *J Pediatr* 2004; **145:** 612–16.
4. Weston S, *et al.* Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005; **90:** 892–7.
5. Fölster-Holst R, *et al.* Prospective, randomized controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; **155:** 1256–61.
6. Anonymous. Probiotics for atopic diseases. *Drug Ther Bull* 2005; **43:** 6–8.
7. Prescott SL, Björkstén B. Probiotics for the prevention or treatment of allergic diseases. *J Allergy Clin Immunol* 2007; **120:** 255–62.

GASTROINTESTINAL DISORDERS. Oral probiotics are under investigation for several gastrointestinal disorders and although they appear to be of benefit in some conditions, further study is required to confirm these findings. It is probable that efficacy depends on the species and strain of the organism as well as on the condition being treated.[1,2]

Conclusions from a systematic review[3] suggest that probiotics might be a useful adjunct to oral rehydration therapy in the treatment of acute infectious *diarrhoea* in adults and children. A meta-analysis[4] of studies of *Lactobacillus* therapy in children reached a similar conclusion. However, it was not possible to draw up definitive treatment guidelines because of a lack of standardisation in probiotic regimens, patient groups, or definition of acute diarrhoea between the available studies.[3,4] Meta-analyses[5,6] and a systematic review[7] of studies investigating the use of probiotics in the prevention of antibiotic-associated diarrhoea in adults[5] and children[5-7] also suggest a beneficial effect, although again, further clinical confirmation is required before they can be routinely recommended.[5-7] A review[8] of studies that looked specifically at treatment or prevention of *Clostridium difficile*-associated diarrhoea with the probiotics *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* concluded that while these specific probiotics might be useful in patients at risk of recurrent *C. difficile* infection, the potential risks of bacteraemia or fungaemia in this particular patient group might outweigh any benefit.

Probiotics have been investigated to correct aberrant intestinal microflora associated with chronic *inflammatory bowel disease* and reviews of such studies suggest some benefit in the prevention and treatment of ulcerative colitis[9-11] and maintenance of remission in pouchitis,[10-12] although the data are not so clear for Crohn's disease.[10,13] Larger controlled clinical studies, again with standardised probiotic preparations and treatment regimens, are necessary to establish the place of probiotics in the management of inflammatory bowel disease.[9-13] Probiotics do not appear to improve abdominal pain in patients with *irritable bowel syndrome* but they may reduce bloating.[14]

Probiotics given to preterm neonates of very low birth-weight reduced the incidence and severity of *necrotising enterocolitis* in 2 randomised controlled studies.[15,16] A systematic review[17] of these and other controlled studies reached the same conclusion, although the authors called for confirmation of these results by a larger study to strengthen the case for routine use of probiotics in preterm neonates.

Probiotics have also been tried in constipation[18] and infantile colic.[19]

1. Anonymous. Probiotics for gastrointestinal disorders. *Drug Ther Bull* 2004; **42:** 85–8.
2. Limdi JK, *et al.* Do probiotics have a therapeutic role in gastroenterology? *World J Gastroenterol* 2006; **12:** 5447–57.
3. Allen SJ, *et al.* Probiotics for treating infectious diarrhoea. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 11/02/08).
4. Van Niel CW, *et al. Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* 2002; **109:** 678–84.
5. D'Souza AL, *et al.* Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* 2002; **324:** 1361–6.
6. Szajewska H, *et al.* Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. *J Pediatr* 2006; **149:** 367–72.
7. Johnston BC, *et al.* Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 11/02/08).
8. Segarra-Newnham M. Probiotics for *Clostridium difficile*-associated diarrhea: focus on *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. *Ann Pharmacother* 2007; **41:** 1212–21.
9. Bai A-P, Ouyang Q. Probiotics and inflammatory bowel diseases. *Postgrad Med J* 2006; **82:** 376–82.
10. Ewaschuk JB, Dieleman LA. Probiotics and prebiotics in chronic inflammatory bowel diseases. *World J Gastroenterol* 2006; **12:** 5941–50.
11. Chapman TM, *et al.* VSL#3 probiotic mixture: a review of its use in chronic inflammatory bowel diseases. *Drugs* 2006; **66:** 1371–87.
12. Sandborn W, *et al.* Pharmacotherapy for induction and maintenance of remission in pouchitis. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 11/02/08).
13. Rolfe VE, *et al.* Probiotics for maintenance of remission in Crohn's disease. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 11/02/08).
14. Bausserman M, Michail S. The use of *Lactobacillus* GG in irritable bowel syndrome in children: a double-blind randomized control trial. *J Pediatr* 2005; **147:** 197–201.
15. Bin-Nun A, *et al.* Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr* 2005; **147:** 192–6.
16. Lin H-C, *et al.* Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005; **115:** 1–4.
17. Deshpande G, *et al.* Probiotics for prevention of necrotising enterocolitis in preterm neonates with very low birthweight: a systematic review of randomised controlled trials. *Lancet* 2007; **369:** 1614–20.
18. Banaszkiewicz A, Szajewska H. Ineffectiveness of *Lactobacillus* GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. *J Pediatr* 2005; **146:** 364–9.
19. Savino F, *et al. Lactobacillus reuteri* (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. *Pediatrics* 2007; **119:** e124-e30. Available at: http:// pediatrics.aappublications.org/cgi/reprint/119/1/e124 (accessed 11/02/08)

UROGENITAL INFECTIONS. Probiotic preparations given orally or intravaginally are under investigation for the prevention or treatment of vaginal infections. Reviews of studies in vulvovaginal candidiasis[1] and bacterial vaginosis[2] concluded that while there was some indication of benefit, larger controlled studies are required to confirm efficacy and the place of probiotics in therapy. A systematic review[3] confirmed that probiotics may be of benefit in the prevention and treatment of bacterial vaginosis in pregnancy but due to insufficient data it was not possible to assess the effect that this might have in preventing preterm labour. A review[4] of studies investigating probiotics for the prevention of urinary-tract infections in women has suggested some benefit.

1. Falagas ME, *et al.* Probiotics for prevention of recurrent vulvovaginal candidiasis: a review. *J Antimicrob Chemother* 2006; **58:** 266–72.
2. Falagas ME, *et al.* Probiotics for the treatment of women with bacterial vaginosis. *Clin Microbiol Infect* 2007; **13:** 657–64.
3. Othman M, *et al.* Probiotics for preventing preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 11/02/08).
4. Falagas ME, *et al.* Probiotics for prevention of recurrent urinary tract infections in women: a review of the evidence from microbiological and clinical studies. *Drugs* 2006; **66:** 1253–61.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Acidofilofago; Flevic; Floratil; Lactinex; Tropivag; ***Austral.:*** Bioglan Acidophilus; Bioglan Superdophilus; Forbiotic; ProTract; ***Austria:*** Antibiophilus; Bioflorin; Lactofit; Reflor; Symbioflor Enterococcus; Yomogi; ***Belg.:*** Enterol; Lacteol; ***Braz.:*** Flomicin; Floratil; Floren; Florent; Lactipan; Leiba; Repoflor; ***Canad.:*** Bacid; Lacidofil; ***Chile:*** Bio-Flora; Biolactus; Econormotil; Gastrofloral; Lacteol Forte†; Lactil; Perenteryl; Perocur†; ***Cz.:*** Enterol; Santax S†; Solco-Trichovac†; ***Denm.:*** Paraghurt; Precosa; ***Fin.:*** Lactophilus; Precosa; ***Fr.:*** Bacilor; Bioprotus; Diarlac†; Gynophilus; Lacteol; Lyo-Bifidus; Ultra-Levure; Ultraderme†; ***Ger.:*** Acidophilus†; Hylak N; Hylak Plus; Infectodiarrstop GG†; Lacteol; Lyseen; Omnisept†; Paidoflor; Perenterol; Symbioflor 1; Vagiflor; ***Gr.:*** Ultra-Levure; ***Hong Kong:*** Bioflor; Lacteol; Reuteri; ***Hung.:*** Enterol; Gynevac; Symbioflor 1; ***India:*** Cefocef-LB; Myconip; Sporlac; ***Indon.:*** Lacbon; Rillus; ***Ital.:*** Bioflorin; Calagin; Codex; Dicoflor; Ecoflorina; Ferlactis†; Inulac; Lab/A†; Lacteol; Lactonorm; Ramno-Flor†; Regolact Plus; Reuflor; ***Mex.:*** Floratil; Lacteol Fort; Lactipan; Lactocil; Lactovita; Lioactil; Neoflor; Sinuberase; ***NZ:*** Blis K12 Throat Guard; ***Philipp.:*** Infloran; ***Pol.:*** Enterol; Lactovaginal; Lakcid†; ***Port.:*** Antibiophilus; Enterol†; Lacteol; UL 250†; ***Rus.:*** Enterol (Энтерол); Gastropharm (Гастрофарм); IRS 19 (ИРС 19); ***S.Afr.:*** Actiflora; Inteflora; ***Singapore:*** DiarrStope; Lacteol; Protexin; Reutefene; ***Spain:*** Casenfilus; Lacteol; Lactofilus; Ultra-Levura; ***Swed.:*** Precosa; ***Switz.:*** Bioflorin; Fiormil†; Florosan; Lacteol†; Lactoferment; Perenterol; SolcoTrichovac Lyophilisat; Ultra-Levure; Ventrux†; ***Thai.:*** Lacbon†; Lacteol†; ***Turk.:*** Reflor; ***UK:*** Bio Acidophilus; Biodophilus; Gum PerioBalance; Infacol Probiotic; ***USA:*** Acidophilus; Bacid; Florastor; Intestinex; Kala; Lactinex; Lacto-Key; MoreDophilus; Pro-Bionate; Superdophilus; ***Venez.:*** Florcidin; Florestor; Lacteol; Lactobacilos; Liolactil; Proflor.

Multi-ingredient: ***Arg.:*** Bioflora; Biol Preo; Factor Bioenterico; Faelac†; Nilflux; Totalflora; Tropivag Plus; ***Austral.:*** Acidophilus Bifidus; Acidophilus Plus; Cyto-Bifidus; ***Austria:*** Gynoflor; Hylak; Hylak Forte; Infloran; Omniflora; Prosymbioflor†; Trevis; ***Belg.:*** Carbolactanose; Gynoflor; ***Canad.:*** Fermalac Vaginal; ***Chile:*** Bion 3; ***Cz.:*** Fermalac Vaginal; Gynoflor; Hylak Forte; Imudon; IRS 19†; Lacidofil; Solco-Urovac†; ***Fr.:*** Actyfilus; Biolactyl; Biotravel; Ergyphilus; Estrofort; Florgynal; Imgalt; Imudon†; IRS 19†; Maxi-Flore; Ophidus; Probionat; Triphidus; Trophigil; Ultrabiotique; ***Ger.:*** Antiprurit†; Gynoflor; InfectoDiarrstop LGG; IRS 19; Omniflora N; Perison; Pro-Symbioflor; StroVac; ***Hong Kong:*** Infloran; Lacspan; Protexin Balance; Protexin Balance+; Protexin Restore; Protexin Vitality; Shin-Biofermin S; ***Hung.:*** Gynoflor; Trevis; ***India:*** ABClox; Ampilox-LB; Amplus; Ampoxin-LB; Bicidal Plus; Bifilac; Biomoxil-LB; Campicillin Plus; Cefix LB; Cephadex LB; Clax; Imox-Clo LB; Lactisyn; LMX; Megaclox LB; Novaclox LB; Novamox LB; Nutrolin-B; Symbiotik; Symoxyl-LB; Vitazyme; Vizylac; ***Indon.:*** Dialac; Gastro-Ad; Lacidofil; Lacto-B; Laktobion; Protexin; Synbio; ***Ital.:*** Al-Flor†; Altaflora Probiotici; Bifilact; Bio Fibralax Bi-Attivo; Bio Flora; Biolactine; Colifagina; Decon Lavanda; Ecofermenti; Endolac; Enterolactis; Enteroseven; Fermenturto-Lio; Floragermina 6; Florbiox†; Florelax; Floren; Floridral; Florvis GG; Gastroenterol; Genefilus F19; Giflorex; Ginil; Infloran; Infloran Bio; Kiri; Lactipan; Lactisporin; Lactivis; Lactogermine; Lactolife; Liozim; Liverton; Neo Lactoflorene; Neogyn; Nepiros; Ninfagin; Psyllogel Fermenti; Ramno Fix; Ramnoflor Plus; Rivuclin; Triacid; Vaxitiol; Yovis; Yovita; ***Jpn:*** The Guard Seichojo; ***Malaysia:*** Hexbio; ***Mex.:*** Neo-Panlacticos; Neo-Panlacticos Plus; Pro-T-Flor; ***Pol.:*** IRS 19; Lacidofil; Trilac; ***Port.:*** Coli-Fagina S; Gynoflor; Infloran†; ***Rus.:*** Acipol (Аципол); Bifiform (Бифиформ); Hylak Forte (Хилак Форте); Imudon (Имудон); Linex (Линекс); SolcoTrichovac (Солкотриховак); ***S.Afr.:*** Culturelle; Culturelle VC; ***Spain:*** Infloran; ***Switz.:*** Gynoflor; Infloran; Ribolac; SolcoTrichovac; ***Thai.:*** Infloran; ***Turk.:*** Gynoflor; ***UK:*** Acidophilus Plus; Beneflora; Culture Care; Fibre Dophilus; Natudophilus; Vinalac; ***USA:*** Acidophilus with Bifidus; Floranex; Pamine FQ Kit; SynBiotics-3; VSL#3; ***Venez.:*** Glutapak-R.

Promelase *(pINN)*

Promelasa; Promélase; Promelasum; Seaprose S.

Промелаза

CAS — 9074-07-1.

Profile

Promelase is an alkaline protease derived from *Aspergillus melleus*. It has been taken by mouth in doses of 30 to 90 mg daily for its supposed benefit in oedema and inflammation associated with trauma, infection, and surgical procedures.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Altan; Flaminase; Mezen†; ***Port.:*** Onoprose†; ***Thai.:*** Korynase†.

Pronase

Profile

Pronase is a mixture of proteinases obtained from *Streptomyces griseus*.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Empynase.

Propolis

Bee Glue; Propóleo; Própolis.

Прополис

Profile

Propolis is a resinous substance collected by bees, primarily, at least in temperate climates, from poplar buds (see also p.2371) and to a lesser extent from conifers. It is mixed with wax by bees and used in the construction and maintenance of their hives. Propolis is composed of resins, balsams, essential and aromatic oils, and pollen, although the exact proportions of each varies from region to region, bee species, and local flora, therefore making standardisation of propolis for medicinal use difficult. Propolis has been reported to have anti-inflammatory and antimicrobial properties. It has been used as a nutritional supplement and in preparations for coughs, mouth disorders, and skin disorders. It has been used as an ointment for the relief of symptoms of herpes labialis. Propolis has also been used in cosmetics and varnishes.

Hypersensitivity reactions have been reported.

◊ For reference to hypersensitivity reactions with bee products, including propolis, see under Royal Jelly, p.2382.

Further references to propolis are given below.

1. Grange JM, Davey RW. Antibacterial properties of propolis (bee glue). *J R Soc Med* 1990; **83:** 159–60.
2. Krol W, *et al.* Synergistic effect of ethanolic extract of propolis and antibiotics on the growth of Staphylococcus aureus. *Arzneimittelforschung* 1993; **43:** 607–9.
3. Volpert R, Elstner EF. Interactions of different extracts of propolis with leukocytes and leukocytic enzymes. *Arzneimittelforschung* 1996; **46:** 47–51.
4. Murray MC, *et al.* A study to investigate the effect of a propolis-containing mouthrinse on the inhibition of de novo plaque formation. *J Clin Periodontol* 1997; **24:** 796–8.

5. Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). *Food Chem Toxicol* 1998; **36:** 347–63.
6. Lieberman HD, *et al.* Allergic contact dermatitis to propolis in a violin maker. *J Am Acad Dermatol* 2002; **46** (suppl): S30–S31.
7. Giusti F, *et al.* Sensitization to propolis in 1255 children undergoing patch testing. *Contact Dermatitis* 2004; **51:** 255–8.
8. Walgrave SE, *et al.* Allergic contact dermatitis from propolis. *Dermatitis* 2005; **16:** 209–15.
9. Majiene D, *et al.* Antifungal and antibacterial activity of propolis. *Curr Nutr Food Sci* 2007; **3:** 304–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Propoleos; ***Austral.:*** Helastop†; ***Chile:*** Propolkit; ***Ger.:*** Propolisept-Salbe; ***Ital.:*** Golapiol; Oral Spray; Pro-30C†; Pro-Gola; Propociclina; Propolcream; ***Pol.:*** Apizel; Propolan; Propolisan; Propolisol; ***USA:*** Probax.

Multi-ingredient: ***Braz.:*** Calmatoss†; Infantoss†; Malvatricin Natural Organic; Proplax†; ***Fr.:*** Pollen Royal†; Propargile; ***Ital.:*** Actires; Altuss; Apistress; Biogreen; Bodyguard; Fosfarsile Forte; Golapiol C; Immumil Plus; Immumil†; Keratolip; Neo-Stomygen; Nepiros; Otosan Natural Ear Drops†; Probigol; Promix 3†; Promix†; Propast; Propomill†; Valda Propoli; ***Switz.:*** Osa gel dentaire aux plantes; ***UK:*** Sinose.

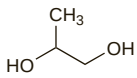
Propylene Glycol

E1520; Glicol Propilênico; Glikol propylenowy; Propilenglicol; Propilénglikol; Propilenglikolis; Propilenoglicol; Propyleeniglykoli; Propylèneglycol; Propylenglycolum; Propylenglykol. (±)-Propane-1,2-diol.

$C_3H_8O_2$ = 76.09.

CAS — 57-55-6 ((±)-propylene glycol); 4254-16-4 ((±)-propylene glycol); 4254-14-2 ((–)-propylene glycol); 4254-15-3 ((+)-propylene glycol).

ATC Vet — QA16QA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Propylene Glycol). A clear, colourless, viscous, hygroscopic liquid. Miscible with water and with alcohol. Store in airtight containers.

USP 31 (Propylene Glycol). A clear, colourless, practically odourless, viscous liquid. It absorbs moisture when exposed to moist air. Miscible with water, with acetone, and with chloroform; soluble in ether; will dissolve in many essential oils but is immiscible with fixed oils. Store in airtight containers.

Adverse Effects and Precautions

Systemic toxicity of propylene glycol is considered to be low after oral doses unless large quantities have been ingested, or when preparations containing propylene glycol are given to neonates or to patients in renal failure. Systemic toxicity is manifested most commonly by CNS depression, especially in neonates and children. Other reported adverse effects include hepatic or renal impairment, intravascular haemolysis, seizures, coma, arrhythmias, and cardiorespiratory arrest. Hyperosmolality has occurred, particularly in small infants and in patients with renal impairment; lactic acidosis may also be a greater problem in the latter group.

After topical use, propylene glycol may produce some local irritation, particularly if applied under occlusive dressings or to mucous membranes; toxicity may occur on application to burns. Hypersensitivity reactions have also been reported. Local sensitivity has been reported after use of ear drops with a propylene glycol vehicle. Injections of preparations containing high concentrations of propylene glycol may produce pain or irritation.

Lactic acidosis. Lactic acidosis developed in a patient with normal renal function given a high-dose continuous lorazepam infusion for which propylene glycol was the principal diluent.[1] Despite temporary resolution of symptoms when the infusion was stopped and bicarbonate given, the patient eventually died. A prospective observational pilot study[2] found propylene glycol to be a common cause of metabolic disturbances in intensive care patients receiving intravenous benzodiazepines, and the authors recommended close monitoring of all such patients.

1. Neale BW, *et al.* Propylene glycol-induced lactic acidosis in a patient with normal renal function: a proposed mechanism and monitoring recommendations. *Ann Pharmacother* 2005; **39:** 1732–6.
2. Wilson KC, *et al.* Propylene glycol toxicity: a severe iatrogenic illness in ICU patients receiving IV benzodiazepines: a case series and prospective, observational pilot study. *Chest* 2005; **128:** 1674–81.

Interactions

Anticoagulants. Propylene glycol has been reported to decrease the effect of *heparin*.[1]

1. Col J, *et al.* Propylene glycol-induced heparin resistance during nitroglycerin infusion. *Am Heart J* 1985; **110:** 171–3.

Pharmacokinetics

Propylene glycol is rapidly absorbed from the gastrointestinal tract. There is evidence of topical absorption when applied to damaged skin.

It is extensively metabolised in the liver primarily by oxidation to lactic and pyruvic acid and is also excreted in the urine unchanged.

◊ References.

1. Yu DK, *et al.* Pharmacokinetics of propylene glycol in humans during multiple dosing regimens. *J Pharm Sci* 1985; **74:** 876–9.
2. Speth PAJ, *et al.* Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. *Ther Drug Monit* 1987; **9:** 255–8.

Uses and Administration

Propylene glycol is widely used in pharmaceutical manufacturing as a solvent and vehicle, especially for drugs unstable or insoluble in water. It may also be used as a stabiliser in vitamin preparations, as a plasticiser, and as a preservative. Propylene glycol is used extensively in foods and cosmetics.

Propylene glycol has humectant properties and is used similarly to glycerol in topical moisturising preparations.

Propylene glycol is used in veterinary medicine as a glucose precursor.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Advanced Eye Relief.

Multi-ingredient: ***Arg.:*** Systane; ***Austral.:*** Dermatech Liquid; ***Austria:*** Acerbine; ***Canad.:*** Episec; Gyne-Moistrin†; Rhinaris; Rhinedrine Moisturizing†; Salinol†; Secaris; Systane; ***Chile:*** Systane; ***Fr.:*** Intrasite; Propy-Lacticare; Systane; ***Ger.:*** Sekudrill†; ***Hong Kong:*** Moisture Eyes; Systane; ***Israel:*** Pedisol†; Taro Gel; ***Ital.:*** Dopo Pik; Sekudrill; Systane; ***Malaysia:*** Systane; ***Mex.:*** Moisture Eyes; Systane; ***Philipp.:*** Moisture Eyes; Systane; ***S.Afr.:*** Aserbine; ***Singapore:*** Systane; ***Spain:*** Acerbiol; ***Switz.:*** Acerbine†; ***Thai.:*** Systane; ***UK:*** Aserbine†; ***USA:*** Astroglide; Biotene with Calcium; Surgel; Zonite; ***Venez.:*** Systane.

Prostaglandins

Profile

The prostaglandins, along with thromboxanes and leukotrienes, are all derived from 20-carbon polyunsaturated fatty acids and are collectively termed *eicosanoids*. In man, the most common precursor is arachidonic acid (eicosatetraenoic acid) whereas eicosapentaenoic acid is a predominant precursor in fish and marine animals.

Arachidonic acid is released from cell-membrane phospholipids by the enzyme phospholipase A_2 and is then rapidly metabolised by several enzymes, the major ones being cyclo-oxygenase (prostaglandin synthetase) and lipoxygenase (see Figure 1, below). The prostaglandins, thromboxanes, and prostacyclin (sometimes collectively termed *prostanoids*) all contain ring structures and are products of arachidonic acid oxidation by cyclo-oxygenase, an enzyme with 2 isoforms (COX-1 or COX-2) widely distributed in cell membranes.

The leukotrienes are products of the lipoxygenase pathway; arachidonic acid is metabolised by lipoxygenases to hydroperoxyeicosatetraenoic acids, which are then further metabolised to leukotrienes.

The initial step in the cyclo-oxygenase pathway is the formation of cyclic endoperoxide prostaglandin G_2 (PGG_2) which is then reduced to the endoperoxide prostaglandin H_2 (PGH_2). Prostaglandin H_2 is then converted to the primary prostaglandins prostaglandin D_2, prostaglandin E_2, and prostaglandin F_2 , to thromboxane A_2 (TXA_2) via the enzyme thromboxane synthetase, or to prostacyclin (PGI_2) via the enzyme prostacyclin synthetase. These products are further metabolised and rapidly inactivated in the body.

The secondary prostaglandins, prostaglandin A_2 (PGA_2), prostaglandin B_2 (PGB_2), and prostaglandin C_2 (PGC_2) are derived from prostaglandin E_2, but are formed during extraction and probably do not occur biologically.

The prostaglandins are all derivatives of the carbon skeleton 7-(2-octilcyclopentyl)heptanoic acid (also known as prostanoic acid). All natural prostaglandins have a double bond at position 1,2 and a hydroxyl group at position 3 of the octil side-chain. Depending on the substitutions on the cyclopentane ring, the main series of prostaglandins are distinguished by the letters A, B, C, D, E, and F; the members of each series are further subdivided by subscript numbers which indicate the degree of unsaturation in the side-chains—hence, those derived from eicosatrienoic acid (dihomo-γ-linolenic acid) have the subscript 1, those derived from arachidonic acid have the subscript 2, and those derived from eicosapentaenoic acid have the subscript 3. In man, only prostaglandins of the '2' series appear to be of physiological importance. Thromboxane A_2 has an oxane rather than a cyclopentane ring; it is chemically unstable and breaks down to thromboxane B_2. Prostacyclin has a double-ring structure and breaks down to 6-keto-prostaglandin F_1 .

Endogenous prostaglandins are autacoids; they can be formed by virtually all tissues and cells in response to a variety of stimuli, have a wide range of **actions**, and are involved in the regulation of virtually all biological functions. Prostaglandins appear to act through various receptor-mediated mechanisms. Some of their effects are mediated within cells by activation or inhibition of adenylate cyclase and the regulation of cyclic adenosine monophosphate production. At one time prostaglandin E_2 and prostaglandin F_2 were thought to be of paramount importance, but with the discovery of thromboxane A_2, prostacyclin, and the leukotrienes it was realised that these primary prostaglandins belong to a large family of physiologically active eicosanoids. Thromboxane A_2 induces platelet aggregation and constricts arterial smooth muscle whereas prostacyclin causes vasodilatation and prevents platelet aggregation; the balance between these opposing actions has an important role in the regulation of intravascular platelet aggregation and thrombus formation. The leukotrienes are important mediators of inflammation.

The pharmacological properties of prostaglandins are wide-ranging and include contraction or relaxation of smooth muscle in the blood vessels, bronchi, uterus, and gastrointestinal tract; inhibition of gastric acid secretion; and effects on platelet aggregation, the endocrine system, and metabolic processes.

Individual prostaglandins vary greatly in their activities and potencies; their actions also depend on the animal species, on the tissues in which they are acting, and on the concentration present, and entirely opposite actions may be elicited with very small structural changes in the molecule.

The diverse **clinical applications** of prostaglandins reflect their wide-ranging physiological and pharmacological properties. Synthetic analogues have been developed with the aim of obtain-

Figure 1. Prostaglandin biosynthesis.