Martindale: The Extra Pharmacopoeia 32th ed.

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Martindale

The complete drug reference

Thirty-second edition

Edited by

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Preface

Over the years Martindale has become much more than the name 'pharmacopoeia' implies and so for this new edition the subtitle 'Extra Pharmacopoeia' has been replaced by 'The Complete Drug Reference'. Martindale is now published every three years. It is also available electronically on CD and as Martindale Online.

The aim of Martindale is to provide practising pharmacists and physicians with unbiased evaluated information on drugs and medicines used throughout the world. It therefore has to develop as the body of knowledge on existing drugs grows, new drugs emerge, new preparations are launched, old preparations abandoned, reformulated, or redefined, and the information needs of those practising pharmacy and medicine continue to evolve. We have tried to ensure that the new edition continues to meet these needs.

All the drug monographs from the last edition have been revised, more than 300 having been deleted and more than 250 added, and organised into chapters that reflect the uses of the drugs being described. One of the new features of this edition is the creation of an Interactions section within drug monographs to make the information more accessible both in the book and electronically. A new Bronchodilators chapter draws together drugs that were formerly described in the Antimuscarinics, Prophylactic Anti-asthma Agents, Sympathomimetics, and Xanthines chapters and includes disease treatment reviews for Asthma and for Chronic Obstructive Pulmonary Disease.

The disease treatment reviews, 644 in all and generally located in the chapter introductions, have also been thoroughly revised in order to reflect current trends and provide key references. Cross-references to these reviews appear in the monographs of the drugs cited; the reviews can also be accessed via the general index. It is hoped that these reviews will be of use to readers who want an overview of a particular disease and its drug treatment and will provide a useful starting point for those who want to pursue particular aspects further.

The information on proprietary preparations, an important feature of Martindale, has been updated and presented more concisely.

Martindale is based on published information and more than 30 000 selected references are included. Our aim is to evaluate the literature, covering important studies, guidelines, and useful reviews and placing them in context. Multicentre studies, meta-analyses, and systematic reviews are playing a growing and important role in the study of drug treatment, and their findings and conclusions are considered in many of our chapters. However, there is also a place for the anecdotal report and the small study, and information from such sources is included where appropriate.

The sheer bulk of Martindale was making it rather unwieldy to use and strenuous editorial efforts have been made this time to reduce the size of the book without sacrificing content.

Martindale is not a book of standards. Inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Arrangement

PART 1 (pages 1–1539) contains 4336 monographs arranged in 51 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. The introductions of those chapters that describe drugs used in the management of disease contain disease treatment reviews—descriptions of those diseases together with reviews of the choice of treatments.

PART 2 (pages 1541–1646) consists of a series of 827 short monographs arranged in the alphabetical order of their main titles. It includes monographs on some new drugs, on drugs not easily classified, on herbals, and on drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

PART 3 (pages 1647–2057) contains proprietary preparations from a range of countries. For this edition we have covered Australia, Austria, Belgium, Canada, France, Germany, Ireland, Italy, the Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, UK, and USA. We have also included some proprietary preparations from Japan. The information provided includes the proprietary name, the manufacturer or distributor, the active ingredients with cross-references to the drug monographs, and a summary of the indications as given by the manufacturer.

Indexes

DIRECTORY OF MANUFACTURERS. In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address if it is available. This directory contains some 5400 entries.

GENERAL INDEX. To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index includes entries for drugs (approved names, synonyms, and chemical names), preparations, pharmacological and therapeutic groups, and clinical uses (disease treatment reviews). As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page.

Nomenclature

MARTINDALE IDENTITY NUMBERS. Each monograph title is followed by an identity number in brackets which consists of a maximum of 6 figures followed by a check character. These numbers are used in our computer manipulation and their purpose is to identify monographs in Martindale.

TITLES AND SYNONYMS. The title of each monograph is in English, with preference being given to British Approved Names (BAN), United States Adopted Names (USAN), and International Nonproprietary Names (INN). These 3 authorities are shown where appropriate. A European Directive (92/27/EEC) requiring the use of Recommended International Nonproprietary Names (rINNs) in the labelling of medicinal products throughout member states of the European Community had not been implemented in the UK at the time of going to press. However, we have acknowledged the move towards replacing BAN by rINN by giving more prominence to INN names. Names given as synonyms include commonly used abbreviated names; Latin versions of *Ph. Eur.* titles; English, American, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. In some approved names it is now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. A table of contracted names for ions and groups used in approved names and titles is given on page xi.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parentheses.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 1995 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry and based on the ^{12}C scale (see page xii). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: Austrian, Belgian, *British*, *British Veterinary*, Chinese, *European*, *French*, *German*, International, Italian, *Japanese*, Netherlands, *Polish*, Portuguese, *Swiss*, and *United States* (including the *Formulary*). Those *italicised* in the above list either appeared as new editions or were revised by supplements since the last edition of Martindale, and have been examined for this 32nd edition.

The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale, see page ix which also includes details of the edition and/or supplement(s) consulted.

Several countries are parties to the Convention on the Elaboration of a European Pharmacopoeia. This means that they must adopt the standards of the European Pharmacopoeia. These countries are currently Austria, Belgium, Bosnia-Herzegovina, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom of Great Britain and Northern Ireland, and the Former Yugoslav Republic of Macedonia. Hence the European Pharmacopoeia is cited in the drug monograph lists of pharmacopoeias rather than these individual national pharmacopoeias.

Official preparations, mainly from the current British and US Pharmacopoeias, are listed at the end of drug monographs.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at temperatures between 15° and 25°. The information usually relates to w/v solubilities but in some cases is v/v if the monograph substance itself is a liquid. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility	
very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. Where authorities differ, we have included the most stringent storage requirement. The term 'a cool place' is generally used to describe a place in which the temperature is between 8° and 15°. In general, the storage conditions apply to the monograph substance and not its solutions or preparations.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Pharmacological and Therapeutic Information

Information on adverse effects, treatment of adverse effects, precautions (including contra-indications), interactions, pharmacokinetics, and uses and administration of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications. This edition contains about 11 300 such abstracts or reviews based on information in an ever widening range of publications.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Manufacturers' literature has been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the fetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when administered by mouth. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v and sodium chloride injection is 0.9% w/v.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

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Martindale staff have been able to call freely on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to JEF Reynolds, DK Mehta and the editorial staff of the British National Formulary, and the staff of the library and information department. Thanks are due to M Davis and EJ Laughton for work on the Preparations database and for other editorial tasks, and also to SL Jefferson and RL Stock who contributed to this edition.

The contents of this 32nd edition were planned, written, checked, indexed, keyed, proofed, and processed by the Martindale staff. The Editor is pleased to acknowledge the skills and commitment of all the Martindale staff and to record her gratitude: to Claire Ryan for clerical assistance and, towards the end of the production cycle, to Evelyn Doh, Pauline Lloyd, and Maria Robinson for a substantial amount of keying; to the Staff Editors Alison Brayfield, Catherine Cadart, Kathleen Eager, Sue Funnell, Prakash Gotecha, Sue Handy, Rhoda Lee, Julie McGlashan, Gail Neathercoat, and Keith Riley; to the Assistant Editors Paul Blake and Anne Parsons; and to the Senior Assistant Editor Sean Sweetman.

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Abbreviations

For abbreviations of the names of manufacturers or their distributors, see Directory of Manufacturers, p.2059.

≈—approximately equals.

ACE—angiotensin-converting enzyme.

agg.—aggregate (in botanical names), including 2 or more species which resemble each other closely.

AIDS—acquired immunodeficiency syndrome.

a.m.—ante meridiem, 'before noon'.

ARC—AIDS-related complex.

Aust.—Austria.

Aust. P.—Austrian Pharmacopoeia 1990 (Österreichisches Arzneibuch) including Addenda 1990 and 1991.

Austral.—Australia.

BAN—British Approved Name.

BANM—British Approved Name Modified.

Belg. P.—Belgian Pharmacopoeia 1980 (Pharmacopée Belge, Sixième Edition) and Supplements to 1988.

BMA—British Medical Association.

BNF—British National Formulary.

b.p.—boiling point.

BP—British Pharmacopoeia. Unless otherwise specified, BP references are to the 1998 edition including Amendments No. 1.

BP (Vet)—British Pharmacopoeia (Veterinary) 1998 and Amendments No. 1.

BPC—British Pharmaceutical Codex.

Br.—British.

BUN—Blood-urea-nitrogen.

°C—degrees Celsius (centigrade). Unless otherwise indicated in the text, temperatures are expressed in this thermometric scale.

C.—*Campylobacter*, *Candida*, *Chlamydia*, or *Corynebacterium*.

Canad.—Canada.

CAPD—continuous ambulatory peritoneal dialysis.

CAS—Chemical Abstracts Service.

CCPD—continuous cycle peritoneal dialysis.

CDC—Centers for Disease Control (USA).

Chin. P.—Chinese Pharmacopoeia 1990.

CI—Colour Index.

CNS—central nervous system.

cP—centipoise(s).

CPMP—Committee on Proprietary Medicinal Products of the European Union.

CRM—the former Committee on the Review of Medicines (UK).

CSF—cerebrospinal fluid.

CSM—Committee on Safety of Medicines (UK).

cSt—centistokes.

D & C—designation applied in USA to dyes permitted for use in drugs and cosmetics.

d.c.—direct current.

DHSS—the former Department of Health and Social Security (UK).

DNA—deoxyribonucleic acid.

DOE—Department of the Environment (UK).

DoH—Department of Health (UK).

DPF—Dental Practitioners' Formulary (UK).

DTF—Drug Tariff Formulary.

ECG—electrocardiogram.

ECT—electroconvulsive therapy.

Ecuad.—Ecuador.

ed.—editor(s) *or* edited by *or* edition.

EEC—European Economic Community, now the European Union.

EEG—electro-encephalogram.

e.g.—*exempli gratia* 'for example'.

ENL—erythema nodosum leprosum.

ENT—ear, nose, and throat.

ESR—erythrocyte sedimentation rate.

ESRD—end-stage renal disease.

et al.—*et alii*, 'and others': for three or more co-authors or co-workers.

EU—European Union.

Eur. P.—see Ph. Eur.

Ext. D & C—designation applied in USA to dyes permitted for use in external drug and cosmetic preparations.

°F—degrees Fahrenheit.

FAC—Food Additives and Contaminants Committee of the Ministry of Agriculture, Fisheries and Food (UK).

FAO—Food and Agriculture Organization of the United Nations.

FAO/WHO—Food and Agriculture Organization of the United Nations *and the* World Health Organization.

FDA—Food and Drug Administration of USA.

FdAC—Food Advisory Committee of the Ministry of Agriculture, Fisheries and Food (UK).

FD & C—designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics.

FEV_1—forced expiratory volume in 1 second.

FIP—Fédération Internationale Pharmaceutique.

f.p.—freezing point.

FPA—Family Planning Association (UK).

Fr.—France.

Fr. P.—French Pharmacopoeia 1982 (Pharmacopée Francaise, X^e Edition) and Supplements 1 to 13.

g—gram(s).

Ger.—Germany.

Ger. P.— German Pharmacopoeia (Deutsches Arzneibuch, 1998).

GFR—glomerular filtration rate.

Hb— haemoglobin.

Hib—*Haemophilus influenzae* type b.

HIV—human immunodeficiency virus.

HLA—human lymphocyte antigens.

HLB—hydrophilic-lipophilic balance.

HSE—Health and Safety Executive (UK).

Hung.—Hungary.

IARC—International Agency for Research on Cancer.

ibid.—*ibidem*, 'in the same place (journal or book)'.

idem—'the same': used for the same authors and titles.

i.e.—*id est*, 'that is'.

Ig—immunoglobulin.

INN—International Nonproprietary Name.

Int. P.—International Pharmacopoeia 3rd ed., Volume 1, 1979; Volume 2, 1981; Volume 3, 1988; and Volume 4, 1994.

IPCS—International Programme on Chemical Safety.

IQ—intelligence quotient.

IR—infra-red.

Irl.—Ireland.

ISO—International Organization for Standardization.

It. P.—Italian Pharmacopoeia 1985 (Farmacopea Ufficiale della Repubblica Italiana, Edizione Nona) and Supplements 1 to 3.

Ital.—Italy.

iu—international unit(s).

IUD—intra-uterine device.

IUPAC—International Union of Pure and Applied Chemistry.

J—joule(s).
Jpn—Japan.
Jpn P.—The Pharmacopoeia of Japan, 13th ed., 1996.
K—kelvin.
kcal—kilocalorie(s).
kg—kilogram(s).
kJ—kilojoule(s).
Kor.—Korea.
lb—pound(s) avoirdupois.
LD_{50}—a dose lethal to 50% of the specified animals or micro-organisms.
Lf—limit flocculation.
m—metre(s).
m^2—square metre(s).
m^3—cubic metre(s).
M—molar.
MAFF—Ministry of Agriculture, Fisheries and Food (UK).
MAOI—monoamine oxidase inhibitor.
max.—maximum.
MBC—minimum bactericidal concentration.
MCA—Medicines Control Agency (UK).
mEq—milliequivalent(s).
mg—milligram(s).
MIC—minimum inhibitory concentration.
min—minute.
min.—minimum.
MJ—megajoule(s).
mL—millilitre(s).
mm—millimetre(s).
mm^2—square millimetre(s).
mm^3—cubic millimetre(s).
mmHg—millimetre(s) of mercury.
mmol—millimole.
mol—mole.
mol. wt—molecular weight.
Mon.—Monaco.
mosmol—milliosmole.
m.p.—melting point.
MRC—Medical Research Council (UK).
µg—microgram(s).
µL—microlitre(s).
µm—micrometre(s).
NCTC—National Collection of Type Cultures (Central Public Health Laboratory, London, England).
Neth.—The Netherlands.
Neth. P.—Netherlands Pharmacopoeia 1983 (Nederlandse Farmacopee, Negende Uitgave) and Supplements to 1993.
ng—nanogram(s).
NIH—National Institutes of Health (USA).
nm—nanometre(s).
Norw.—Norway.
NSAID—nonsteroidal anti-inflammatory drug.
OP—over proof.
o/w—oil-in-water.
P—probability.
Pa—pascal(s).
PBI—protein-bound iodine.
pCO_2—plasma partial pressure (concentration) of carbon dioxide.
p_aCO_2—arterial plasma partial pressure (concentration) of carbon dioxide.
pg—picogram(s).
pH—the negative logarithm of the hydrogen ion concentration.
Ph. Eur.—European Pharmacopoeia, 3rd ed., 1997 and Supplements 1998 and 1999.
Pharm. Soc. Lab. Rep.—Royal Pharmaceutical Society's Laboratory Report.
PHLS—Public Health Laboratory Service (UK).
pINN—Proposed International Nonproprietary Name.
pINNM—Proposed International Nonproprietary Name Modified.
pK_a—the negative logarithm of the dissociation constant.
p.m.—*post meridiem*, 'afternoon'.
pO_2—plasma partial pressure (concentration) of oxygen.
p_aO_2—arterial plasma partial pressure (concentration) of oxygen.
Pol.—Poland.
Pol. P.—Polish Pharmacopoeia (Farmakopea Polska) 5th ed., Volume 1, 1990; Volume 2, 1993; Supplement 1, 1995; Volume 3, 1996.
Port.—Portugal.
Port. P.—Portuguese Pharmacopoeia 1986 (Farmacopoeia Portuguesa V) and Supplements to 1991.
ppm—parts per million.
PSGB—The Pharmaceutical Society of Great Britain. Now the Royal Pharmaceutical Society of Great Britain.
q.s.—*quantum sufficit*, 'as much as suffices'.
q.v.—*quod vide*, 'which see'.
RCGP—Royal College of General Practitioners (UK).
RIMA—reversible inhibitor of monoamine oxidase type A.
rINN—Recommended International Nonproprietary Name.
rINNM—Recommended International Nonproprietary Name Modified.
RNA—ribonucleic acid.
RPSGB—The Royal Pharmaceutical Society of Great Britain.
S. Afr.—South Africa.
SGOT—serum glutamic oxaloacetic transaminase (serum aspartate aminotransferase *now preferred*).
SGPT—serum glutamic pyruvic transaminase (serum alanine aminotransferase *now preferred*).
SI—Statutory Instrument *or* Système International d'Unités (International System of Units).
SLE—systemic lupus erythematosus.
sp.—species (plural spp.).
sp. gr.—specific gravity.
SSRI—selective serotonin reuptake inhibitor.
St—stokes.
subsp.—subspecies.
suppl—supplement(s).
Swed.—Sweden.
Swiss P.—Swiss Pharmacopoeia 1997 (Pharmacopoea Helvetica, 8^e édition, Edition Française) and Supplement 1998.
Switz.—Switzerland.
Thai.—Thailand.
TPN—total parenteral nutrition.
UK—United Kingdom.
UNICEF—United Nations Children's Fund.
UP—under proof.
US and **USA**—United States of America.
USAN—United States Adopted Name.
USNF—The United States 'National Formulary 18', 1995, and Supplements 1 to 9.
USP—The United States Pharmacopeia 23, 1995, and Supplements 1 to 9.
UV—ultraviolet.
var.—variety.
vol.—volume(s).
v/v—volume in volume.
v/w—volume in weight.
WHO—World Health Organization.
w/o—water-in-oil.
wt—weight.
wt per mL—weight per millilitre.
w/v—weight in volume.
w/w—weight in weight.

Contracted Names for Ions and Groups

Contracted Name	Chemical Name
acetonide	isopropylidene ether of a dihydric alcohol
aceturate	*N*-acetylglycinate
acistrate	2′-acetate (ester) and stearate (salt)
acoxil	acetoxymethyl
amsonate	4,4′-diaminostilbene-2,2′-disulphonate
anisatil	2-(4-methoxyphenyl)-2-oxoethyl
axetil	1-acetoxyethyl
besylate (besilate)	benzenesulphonate
bezomil	(benzoyloxy)methyl
buciclate	*trans*-4-butylcyclohexanecarboxylate
bunapsilate	3,7-di-*tert*-butylnaphthalene-1,5-disulphonate
buteprate	17-(1-oxobutoxy) (ester) and 21-(1-oxopropoxy) (ester)
camsylate (camsilate)	camphor-10-sulphonate
caproate	hexanoate
carbesilate	4-carboxybenzenesulphonate
cilexetil	(*RS*)-1-{[(cyclohexyloxy)carbonyl]oxy}ethyl
closylate (closilate)	4-chlorobenzenesulphonate
crobefate	(±)-(*E*)-6-hydroxy-4′-methoxy-3-(*p*-methoxybenzylidene)flavone phosphate ion (2–)
cromacate	[(6-hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetate
cromesilate	6,7-dihydroxycoumarin-4-methanesulphonate
cyclotate (ciclotate)	4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylate
cypionate (cipionate)	3-cyclopentylpropionate
deanil	2-dimethylaminoethyl
dibudinate	2,6-di-*tert*-butylnaphthalene-1,5-disulphonate
dibunate	2,6-di-*tert*-butyl-1-naphthalenesulphonate
digolil	2-(2-hydroxyethoxy)ethyl
diolamine	diethanolamine
dipivoxil	(2,2-dimethyl-1-oxopropoxy)methyl or (pivaloyloxy)methyl (=pivoxil)
dofosfate	octadecyl hydrogen phosphate
edamine	ethylenediamine
edetate	ethylenediamine-*NNN′N′*-tetra-acetate
edisylate (edisilate)	ethane-1,2-disulphonate
embonate	4,4′-methylenebis(3-hydroxy-2-naphthoate) (=pamoate)
enanthate (enantate)	heptanoate
epolamine	1-pyrrolidineethanol
erbumine	*tert*-butylamine
estolate	propionate dodecyl sulphate
esylate (esilate)	ethanesulphonate
etabonate	(ethoxycarbonyl)oxy (=ethyl carbonate)
farnesil	(2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienyl
fendizoate	2-[(2′-hydroxy-4-biphenylyl)carbonyl]benzoate
fostedate	tetradecyl hydrogen phosphate
gluceptate	glucoheptonate
hybenzate (hibenzate)	2-(4-hydroxybenzoyl)benzoate
hyclate	monohydrochloride hemi-ethanolate hemihydrate
isethionate (isetionate)	2-hydroxyethanesulphonate
lauryl sulphate (laurilsulfate)	dodecyl sulphate
megallate	3,4,5-trimethoxybenzoate
meglumine	*N*-methylglucamine
mesylate (mesilate)	methanesulphonate
metembonate	4,4′-methylenebis(3-methoxy-2-naphthoate)
mofetil	2-(morpholino)ethyl
napadisylate (napadisilate)	naphthalene-1,5-disulphonate
napsylate (napsilate)	naphthalene-2-sulphonate
olamine	ethanolamine
oxoglurate	2-oxoglutarate
pamoate	4,4′-methylenebis(3-hydroxy-2-naphthoate) (=embonate)
pendetide	N^6-{*N*-[2-({2-[bis(carboxymethyl)amino]-ethyl}(carboxymethyl)amino)ethyl]-*N*-(carboxymethyl)glycyl}-N^2-(*N*-glycyl-L-tyrosyl)-L-lysine
pentexil	1-hydroxyethyl pivalate
phenpropionate	3-phenylpropionate
pivalate	trimethylacetate
pivoxetil	1-(2-methoxy-2-methylpropionyloxy)ethyl
pivoxil	(2,2-dimethyl-1-oxopropoxy)methyl or (pivaloyloxy)methyl (=dipivoxil)
polistirex	sulphonated styrene-divinylbenzene copolymer complex
proxetil	1-[(isopropoxycarbonyl)oxy]ethyl
steaglate	stearoyloxyacetate
suleptanate	sodium 7-[methyl(2-sulphonatomethyl)carbamoyl]heptanoyl
tebutate	*tert*-butylacetate
tenoate	2-thiophenecarboxylate
teprosilate	3-(theophyllin-7-yl)propanesulphonate
theoclate (teoclate)	8-chlorotheophyllinate
tofesilate	2-(theophyllin-7-yl)ethanesulphonate
tosylate (tosilate)	toluene-4-sulphonate
triclofenate	2,4,5-trichlorophenolate
triflutate	trifluoroacetate
trolamine	triethanolamine
troxundate	3,6,9-trioxaundecanoate
xinafoate	1-hydroxy-2-naphthoate

Atomic Weights of the Elements—$^{12}C=12$

Atomic Number	Name	Symbol	Atomic Weight
89	Actinium	Ac	*
13	Aluminium	Al	26.981538
95	Americium	Am	*
51	Antimony	Sb	121.760
18	Argon	Ar	39.948
33	Arsenic	As	74.92160
85	Astatine	At	*
56	Barium	Ba	137.327
97	Berkelium	Bk	*
4	Beryllium	Be	9.012182
83	Bismuth	Bi	208.98038
5	Boron	B	10.811
35	Bromine	Br	79.904
48	Cadmium	Cd	112.411
55	Caesium	Cs	132.90545
20	Calcium	Ca	40.078
98	Californium	Cf	*
6	Carbon	C	12.0107
58	Cerium	Ce	140.116
17	Chlorine	Cl	35.4527
24	Chromium	Cr	51.9961
27	Cobalt	Co	58.933200
29	Copper	Cu	63.546
96	Curium	Cm	*
66	Dysprosium	Dy	162.50
99	Einsteinium	Es	*
68	Erbium	Er	167.26
63	Europium	Eu	151.964
100	Fermium	Fm	*
9	Fluorine	F	18.9984032
87	Francium	Fr	*
64	Gadolinium	Gd	157.25
31	Gallium	Ga	69.723
32	Germanium	Ge	72.61
79	Gold	Au	196.96655
72	Hafnium	Hf	178.49
2	Helium	He	4.002602
67	Holmium	Ho	164.93032
1	Hydrogen	H	1.00794
49	Indium	In	114.818
53	Iodine	I	126.90447
77	Iridium	Ir	192.217
26	Iron	Fe	55.845
36	Krypton	Kr	83.80
57	Lanthanum	La	138.9055
103	Lawrencium	Lr	*
82	Lead	Pb	207.2
3	‡Lithium	Li	6.941
71	Lutetium	Lu	174.967
12	Magnesium	Mg	24.3050
25	Manganese	Mn	54.938049
101	Mendelevium	Md	*
80	Mercury	Hg	200.59
42	Molybdenum	Mo	95.94
60	Neodymium	Nd	144.24
10	Neon	Ne	20.1797
93	Neptunium	Np	*
28	Nickel	Ni	58.6934
41	Niobium	Nb	92.90638
7	Nitrogen	N	14.00674
102	Nobelium	No	*
76	Osmium	Os	190.23
8	Oxygen	O	15.9994
46	Palladium	Pd	106.42
15	Phosphorus	P	30.973761
78	Platinum	Pt	195.078
94	Plutonium	Pu	*
84	Polonium	Po	*
19	Potassium	K	39.0983
59	Praseodymium	Pr	140.90765
61	Promethium	Pm	*
91	†Protactinium	Pa	231.03588
88	Radium	Ra	*
86	Radon	Rn	*
75	Rhenium	Re	186.207
45	Rhodium	Rh	102.90550
37	Rubidium	Rb	85.4678
44	Ruthenium	Ru	101.07
62	Samarium	Sm	150.36
21	Scandium	Sc	44.955910
34	Selenium	Se	78.96
14	Silicon	Si	28.0855
47	Silver	Ag	107.8682
11	Sodium	Na	22.989770
38	Strontium	Sr	87.62
16	Sulphur	S	32.066
73	Tantalum	Ta	180.9479
43	Technetium	Tc	*
52	Tellurium	Te	127.60
65	Terbium	Tb	158.92534
81	Thallium	Tl	204.3833
90	†Thorium	Th	232.0381
69	Thulium	Tm	168.93421
50	Tin	Sn	118.710
22	Titanium	Ti	47.867
74	Tungsten	W	183.84
109	Unnilennium	Une	*
106	Unnilhexium	Unh	*
108	Unniloctium	Uno	*
105	Unnilpentium	Unp	*
104	Unnilquadium	Unq	*
107	Unnilseptium	Uns	*
110	Ununnilium	Uun	*
111	Unununium	Uuu	*
92	†Uranium	U	238.0289
23	Vanadium	V	50.9415
54	Xenon	Xe	131.29
70	Ytterbium	Yb	173.04
39	Yttrium	Y	88.90585
30	Zinc	Zn	65.39
40	Zirconium	Zr	91.224

Elements marked (*) have no stable nuclides and IUPAC states "there is no general agreement on which of the isotopes of the radioactive elements is, or is likely to be judged 'important' and various criteria such as 'longest half-life', 'production in quantity', 'used commercially', etc., have been applied in the Commission's choice." However, atomic weights are given for radioactive elements marked (†) as they do have a characteristic terrestrial isotopic composition. Commercially available lithium (‡) materials have atomic weights ranging from 6.94 to 6.99; if a more accurate value is required, it must be determined for the specific material.

Contents

Part I

Monographs on Drugs and Ancillary Substances

Analgesics Anti-inflammatory Drugs and Antipyretics

The compounds described in this chapter are used mainly in the relief of pain, inflammation and, sometimes, fever. They can be grouped broadly into one of the categories briefly described below.

Gold compounds

Gold compounds are used mainly for their anti-inflammatory effect in active progressive rheumatoid arthritis and progressive juvenile chronic arthritis; they may also be beneficial in psoriatic arthritis. The mechanism of action of gold compounds in rheumatic disorders is as yet unknown.

For further discussion of the actions and uses of gold compounds, see Sodium Aurothiomalate, p.83.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of unrelated organic acids that have analgesic, anti-inflammatory, and antipyretic properties. NSAIDs are inhibitors of the enzyme cyclo-oxygenase, which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p.1411 and p.704). There are 2 forms of cyclo-oxygenase, COX-1, which is the constitutive form of the enzyme, and COX-2, which is the form induced in the presence of inflammation. Inhibition of COX-2 is therefore thought to be responsible for at least some of the analgesic, anti-inflammatory, and antipyretic properties of NSAIDs whereas inhibition of COX-1 is thought to produce some of their toxic effects, particularly those on the gastro-intestinal tract. Most of the NSAIDs currently available for clinical use inhibit both COX-1 and COX-2.

Aspirin (see under Salicylates, below) is also considered to be an NSAID, but it irreversibly acetylates cyclo-oxygenase whereas other NSAIDs compete with arachidonic acid at the active site of cyclo-oxygenase.

NSAIDs are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile chronic arthritis, and ankylosing spondylitis. Indomethacin and some other NSAIDs are used to close patent ductus arteriosus in premature neonates. Some NSAIDs are applied topically for the relief of muscular and rheumatic pain, and some are used in ophthalmic preparations for ocular inflammatory disorders.

For further discussion of the actions and uses of NSAIDs, see p.63.

Opioid Analgesics

Opioid analgesics include the opium alkaloids morphine and codeine and their derivatives as well as synthetic substances with agonist, partial agonist, or mixed agonist-antagonist activity at opioid receptors. The term opiate analgesics refers only to those opioids derived from opium, or their semisynthetic congeners. The term narcotic analgesic has legal connotations and is no longer used pharmacologically or clinically.

The majority of opioids are used as analgesics, and morphine is the standard against which all other opioid analgesics are compared. Weak opioids such as codeine or dextropropoxyphene are used in the treatment of moderate to severe pain, and are often combined with non-opioid analgesics such as aspirin, other NSAIDs, or paracetamol. Strong opioids such as morphine are used in severe acute and chronic pain, including cancer pain. Some opioids such as codeine, morphine, and diamorphine are also used as antitussives, although the latter two are usually reserved for use in terminal lung disease. Some opioid analgesics such as fentanyl and its congeners are used mainly as adjuncts to anaesthesia; some of these may also be used in higher doses as the sole anaesthetic drug. Opioids with these uses are described in this chapter.

Opioids such as dextromethorphan and pholcodine that are used exclusively as antitussives are discussed under Cough, p.1052. Opioids such as diphenoxylate and loperamide that are used exclusively in the treatment of diarrhoea are discussed under Gastro-intestinal Drugs, p.1167.

Opioids can produce physical dependence and withdrawal symptoms on sudden discontinuation. They are also subject to abuse.

For further discussion of the actions and uses of Opioid Analgesics, see p.67.

Para-aminophenol derivatives

Paracetamol is the principal para-aminophenol derivative in use. Acetanilide (p.12) and phenacetin (p.78) were formerly used but have generally been replaced by safer analgesics. Propacetamol (p.81) is hydrolysed to paracetamol in the plasma.

Paracetamol has analgesic and antipyretic properties and weak anti-inflammatory activity. The mechanism of analgesic action remains to be fully elucidated, but may be due to inhibition of prostaglandin synthesis both centrally and peripherally. Paracetamol is used for the relief of mild to moderate pain and minor febrile conditions.

Benorylate (p.21) is an ester of aspirin and paracetamol with similar uses as the individual components.

For further discussion of the actions and uses of paracetamol, see p.72.

Salicylates

Aspirin and other salicylates are NSAIDs (see above) and have analgesic, anti-inflammatory, and antipyretic properties. They are inhibitors of the enzyme cyclo-oxygenase, which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p.1411 and p.704). Salicylates are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile chronic arthritis, and ankylosing spondylitis. Some salicylates are applied topically in rubefacient preparations for the relief of muscular and rheumatic pain. Aspirin also inhibits platelet aggregation and is used in cardiovascular disorders. Non-acetylated salicylates do not have antiplatelet activity.

Benorylate (p.21) is an ester of aspirin and paracetamol with similar uses as the individual components.

For further discussion of the actions and uses of salicylates, see Aspirin, p.16.

Fever and hyperthermia

The hypothalamus is the centre of the thermoregulatory system and is responsible for maintaining the body temperature at a set point (known as the set-point temperature) which is normally 37°. Mechanisms which produce or conserve body heat include passive heat absorption from the environment, peripheral vasoconstriction, and thermogenic processes such as metabolic reactions and shivering. Heat loss is achieved mainly through sweating and peripheral vasodilatation. Body temperature may be elevated by a number of causes and it is important to distinguish between these as the appropriate treatment may vary according to the mechanisms of the temperature increase.

Fever (pyrexia) is defined as an increase in body temperature due to an elevated thermoregulatory set-point temperature. Common causes of fever include infections, inflammatory disorders, neoplastic disease, and some drug treatment. The term hyperthermia (hyperpyrexia) has been used when the set point is not altered, but there is a disturbance of thermoregulatory control. This may be due to injury to the hypothalamus, defective heat loss as occurs in dehydration, or excessive heat production following strenuous activities or as a reaction to certain drugs such as anaesthetics (malignant hyperthermia) or antipsychotics (neuroleptic malignant syndrome).

Treatment of fever. Whenever possible the underlying cause of the fever should be identified and treated first.[1] Apart from pregnant women or patients who are already dehydrated or malnourished or those with cardiac, respiratory, or neurological diseases, body temperatures up to 41° are relatively harmless.[1] It is not clear if there is any value in treating fever at lower temperatures. Antipyretics have been given to febrile children but studies have shown that such treatment did not necessarily improve their comfort[2] and might even prolong any infection.[3] It has also been suggested[4] that in severe infection the use of antipyretics might increase mortality. It has been noted[4] that the WHO recommend that in developing countries antipyretics should not be given routinely to children with fever; they should be reserved for those with severe discomfort or high fever. In the UK, antipyretic therapy is recommended to treat post-immunisation fever developing after some vaccines.[5] However, if the fever persists after the second dose of antipyretic medical advice should be sought. Antipyretics have also been given as prophylaxis against febrile convulsions, especially in those with a previous history of such seizures or in those with epilepsy. However, antipyretic therapy does not appear to prevent recurrence of febrile convulsions (p.338).[1,6,7] There is also little to support the use of antipyretics for prophylaxis of post-immunisation fever although some suggest offering it to infants at higher risk of seizures receiving diphtheria-tetanus-pertussis or polio immunisation.[5]

Methods for reducing body temperature in fever include the use of antipyretics and/or physical means. Dissipation of body heat may be aided by removing excess clothing or bedding, maintaining a cool environment, and avoiding movement. Maintaining an adequate fluid intake is important. Fanning and tepid sponging are often employed although opinion on their value varies.[1,6,8] Cold baths should not be used as they may actually increase body temperature by inducing vasoconstriction. One study has suggested that antipyretics may be more effective than physical methods for reducing fever in children but the best response was obtained using an antipyretic with tepid sponging.[8] Antipyretics used include paracetamol, salicylates such as aspirin and some other NSAIDs. In fever they appear to promote the return of the set-point temperature to nor-

mal by inhibiting central synthesis and release of prostaglandins that mediate the effect of endogenous pyrogens in the hypothalamus. They cannot lower the body temperature below normal and are ineffective against raised body temperature not associated with fever. Some NSAIDs such as indomethacin and naproxen may be of value both for the differential diagnosis and the management of neoplastic fever as they appear to be more effective in reducing this type of fever than against fever associated with infections.

Paracetamol is usually the antipyretic of choice in infants and children; salicylates are generally contra-indicated in these patients because of the possible link between their use and the development of Reye's syndrome. Ibuprofen appears to be as effective as paracetamol[9] and may be of use when an alternative is required,[10] but there is still relatively little experience of its use and safety in infants and children.

Treatment of hyperthermia. Hyperthermia may produce body temperatures greater than 41°. It can result from heat stroke which may be an extreme form of exertional hyperthermia or may occur when there is an underlying thermoregulation defect, usually in sedentary, elderly subjects. Other causes include drug-induced hyperthermia and thyrotoxic crisis. Hyperthermia can also be induced by a number of drugs either during normal usage or following overdosage. Hyperthermia associated with anaesthesia is discussed under malignant hyperthermia (p.1314). Hyperthermia associated with antipsychotics is discussed under neuroleptic malignant syndrome (p.651). Some drugs that can cause hyperthermia in overdosage include antimuscarinics, salicylates, amphetamines, MAOIs, and cocaine. As with fever, the underlying causes should be identified and treated with appropriate supportive care. These high temperatures are life-threatening and should be lowered immediately. One of the most rapid and effective means of cooling is to immerse the patient in very cold water but core temperature should be monitored to avoid inducing hypothermia.[11] Some consider evaporative cooling methods to be more efficient.[12] Intravenous or intraperitoneal administration of cool fluids, gastric lavage or enemas with ice water have also been used.[11,13] Antipyretics are ineffective since the high temperatures are a result of thermoregulatory failure.

When hyperthermia is associated with muscle rigidity and fulminant hypermetabolism of skeletal muscle, as in the neuroleptic malignant syndrome and malignant hyperthermia, temperature reductions may be obtained using the muscle relaxant dantrolene. There is also anecdotal evidence that dantrolene may produce beneficial effects for the treatment of similar symptoms resulting from poisoning with various agents but the manufacturers have warned physicians that they should not regard dantrolene as an effective treatment for all types of hyperthermia and rigidity accompanying poisoning. In severe cases of hyperthermia when neuromuscular hyperactivity may also impair ventilation a neuromuscular blocker has been used, although suxamethonium is best avoided as it can itself precipitate malignant hyperthermia. Although experience in a small number of patients suggests that dantrolene can hasten cooling in patients with heat stroke when used with conventional cooling methods there is no evidence that it affects outcome.[14]

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Musculoskeletal and joint disorders

The **rheumatic disorders** are a wide range of painful disorders affecting primarily the joints and related structures of the musculoskeletal system, but there may also be widespread involvement of other systems. The term arthritis is used when the disease is largely confined to the joints. Some of the most common forms of arthritis are discussed in this section and these include rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, and the spondyloarthropathies such as ankylosing spondylitis. Other conditions that are associated with arthritis and which are discussed elsewhere include gout (p.390) and systemic lupus erythematosus (p.1029).

The names **soft-tissue rheumatism** (see below) and non-articular rheumatism, have been used to describe a number of painful conditions associated with disease of the structures that surround a joint. For a discussion of the management of **low back pain**, see below.

Juvenile chronic arthritis. Juvenile chronic arthritis is a term used to describe a clinically heterogeneous group of idiopathic arthritides occurring in children under 16 years of age.

Methods of treatment are generally the same as for rheumatoid arthritis in adults (see below), although for some drugs there is limited experience of their use in children. Juvenile chronic arthritis is one of the limited number of indications for the use of aspirin in children.

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Osteoarthritis. Osteoarthritis is a diverse collection of diseases also known as osteoarthrosis, degenerative joint disease, or joint failure. It is characterised by progressive disintegration of articular cartilage, usually accompanied by new bone formation at joint margins and beneath the involved cartilage. There may be synovial inflammation, particularly in advanced disease, but it is different in nature to that seen with rheumatoid arthritis and is usually only a minor component of the disease. Osteoarthritis may be a sequel to trauma, inflammation, or metabolic disorders, but usually the underlying origin is not apparent.

Although there have been claims based largely on *animal* studies that various drugs are chondroprotective, there is no evidence from controlled studies in humans that any treatment is disease-modifying. Management is therefore aimed at relief of pain and maintenance of joint function.

Physical methods of treatment include physiotherapy, heat and cold therapy, exercises, splinting, and weight reduction in the obese. Acupuncture and transcutaneous electrical nerve stimulation (TENS) are also used in the management of osteoarthritis.

A non-opioid analgesic such as paracetamol is usually tried first for the relief of pain. An NSAID may be tried when paracetamol is ineffective or when there is a significant inflammatory component but there is the risk of adverse effects with prolonged use of NSAIDs, especially in the elderly. There has also been concern that NSAIDs such as indomethacin may accelerate osteoarthritis. When the use of NSAIDs is considered essential misoprostol is sometimes administered concurrently in an attempt to reduce gastro-intestinal adverse effects such as peptic ulceration and haemorrhage. Weak opioids such as codeine or dihydrocodeine are sometimes used in combination with paracetamol if the pain is unresponsive to paracetamol alone. Topical analgesics such as NSAIDs or capsaicin, or rubefacients may provide slight relief of pain but their role, if any, is unclear. Systemic corticosteroids have no place in the management of osteoarthritis. Intra-articular or peri-articular injections of corticosteroids are somewhat controversial but may be of help in some patients with localised inflammation, although if used they should only be given infrequently and as adjunctive therapy.

Surgery, including joint replacement, is of great benefit to patients with severe osteoarthritis that cannot be effectively managed by physical or medical therapy.

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Rheumatoid arthritis. Rheumatoid arthritis is a common chronic systemic inflammatory disease that predominantly affects the synovial joints and results in progressive diability and increased mortality. Early rheumatoid arthritis is characterised primarily by inflammation of the synovium; as the disease progresses the patient suffers destruction of cartilage and bone. Extra-articular features commonly include general malaise, fatigue, weight loss, fever, and anaemia. Features associated with more severe forms of the disease include vasculitis, pericarditis, pleurisy, pleural effusion, pulmonary interstitial fibrosis, peripheral neuropathies, subcutaneous and pulmonary nodules, scleritis, and Sjögren's syndrome. Palindromic rheumatism is characterised by repeated episodes of arthritis and periarthritis without fever; the joints appear normal between attacks.

The cause of rheumatoid arthritis is probably multifactorial. There may well be an immunological component because about 80% of patients with rheumatoid arthritis have raised serum concentrations of rheumatoid factors, which are antibodies directed against immunoglobulin G (IgG). However, these antibodies are also found in other diseases and their role is unclear in the pathogenesis of rheumatoid arthritis. Another hypothesis proposes that rheumatoid arthritis may be the result of some infectious agent. Whatever the initial trigger, evidence is accumulating that release of cytokines such as tumour necrosis factor alpha (TNF-α) and interleukins (IL-1 and IL-6) following activation of T-lymphocytes by unknown antigens and macrophages maintain the chronic systemic and synovial inflammation characteristic in rheumatoid arthritis.

The incidence of rheumatoid arthritis is initially higher in women than in men but equalises in later life, and it has been suggested that androgens may have some sort of protective effect.

The severity and course of the disease varies greatly between patients. Disease activity usually fluctuates during the first few months and it is difficult to predict the course of the disease at this stage. Some patients will have a mild disease and may only experience brief attacks with little or no disease progression. However, the vast majority of patients will have intermittent relapses and remissions with an overall pattern of slowly progressive joint destruction and deformity. A few patients may have very severe and rapidly progressive disease.

Since there is no curative treatment for rheumatoid arthritis, management is aimed at alleviating pain and improving or maintaining joint function. This is accomplished through physiotherapy as well as the use of drugs. In some cases surgery may be required.

The choice of drugs for relief of pain depends upon the severity of symptoms. In mild cases an analgesic such as paracetamol may be all that is required but most patients need the additional anti-inflammatory effect provided by an NSAID. Although there is little apparent difference between the various NSAIDs in terms of anti-inflammatory activity, patient responses vary widely. When starting an NSAID the dose should be gradually increased to the recommended maximum over one to two weeks; if the response is inadequate after a total of about four weeks, or if adverse effects are intolerable, other NSAIDs should be tried. Misoprostol is sometimes administered with NSAIDs in an attempt to reduce gastro-intestinal adverse effects such as peptic ulceration and haemorrhage. Topical analgesics such as

NSAIDs or capsaicin, or rubefacients may provide slight relief of pain but their role, if any, is unclear.

Although NSAIDs provide symptomatic relief they do not affect the release of cytokines in conventional doses and therefore do not suppress the rate of cartilage erosion or alter the course of the disease. Because of the risks of toxicity the use of disease modifying antirheumatic drugs (DMARDs) (also referred to as second-line drugs) had conventionally been delayed until there was overt evidence of progressive disease but it is now clear that irreversible joint damage commonly occurs early in the disease and many rheumatologists now add a DMARD shortly after rheumatoid arthritis has been diagnosed in order to try and arrest or slow this deterioration.[1] There is some evidence from controlled studies[2,3] to indicate that early aggressive treatment can improve prognosis, at least in the short-term, but whether it should be given to all patients with very early disease remains to be determined.[4] It is also unclear whether early use of DMARDs will reduce long-term disability[1] but a recent multicentre study[5] has indicated their potential; data from 2888 patients with rheumatoid arthritis followed up for an average of 9 years, indicated that consistent use of DMARDs is associated with an improvement in long-term functional outcomes,[5] compared with patients who had used such drugs inconsistently.

DMARDs are a diverse group with different structures and probably different modes of action; they include the antimalarials (chloroquine, hydroxychloroquine), sulphasalazine, gold compounds (auranofin, sodium aurothiomalate), penicillamine, methotrexate, azathioprine, cyclophosphamide, and cyclosporin. It is thought that the mechanism of action of most of the DMARDs may involve blockade of the release or activity of cytokines to some degree, although other mechanisms may also be involved; current hypotheses on the modes of action of some have been discussed.[6] DMARDs have been referred to as slow-acting antirheumatic drugs as, unlike the NSAIDs, any therapeutic effect may not be apparent for 4 to 6 months. If, however, the response is inadequate after at least 6 months of therapy another DMARD should be tried.

The long-term use of DMARDs is limited by toxicity and loss of efficacy. Many patients do not continue to take a particular drug for more than one or two years. Discontinuation of therapy in a patient who has shown improvement may initiate a relapse. However, drug withdrawal may be considered by some clinicians for patients in complete remission, although evidence for the benefit of either continuing or discontinuing DMARDs in such patients is lacking.[7] In a randomised, placebo-controlled study[8] of stopping DMARDs in rheumatoid arthritis, the risk of synovitis was doubled in patients who discontinued active therapy. In the authors' opinion, DMARDs should be continued in patients with a good response as the risk of adverse effects during long-term therapy was observed to be low. However, since 62% of the placebo group went for a full year without experiencing a rheumatoid flare, it may be reasonable for some patients to consider stopping treatment. In a further study[9] in patients who had discontinued DMARDs, restarting therapy with the same antirheumatic drug when the disease flared up again was effective in most cases.

As adverse reactions with DMARDs frequently occur and may be life threatening, all patients require careful monitoring to avoid severe toxicity.[10,11] Patients who relapse during treatment with one DMARD may gain benefit when a different one is substituted. Treatment with more than one DMARD in various regimens is being tried but there is little available evidence to assess benefit.[1] A meta-analysis[12] of 5 different combinations of DMARDs found that although efficacy might be greater than single DMARDs, toxicity was also increased. However some combinations have produced favourable results.

There is little agreement on which DMARD should be used first and their selection is largely based on individual experience and preference. At present, data from comparative studies are insufficient to allow more than a crude ranking of the DMARDs with regard to efficacy and toxicity, but a number of reviews and analyses have been published to aid the rational selection of these drugs in rheumatoid arthritis.[1,13-23] Some meta-analyses[13,15] of generally short-term comparative studies suggest that methotrexate, intramuscular gold (sodium aurothiomalate), sulphasalazine, and penicillamine are more or less equivalent in efficacy, while the antimalarials and oral gold (auranofin) appear to be somewhat less effective. Intramuscular gold exhibited the highest toxicity while the antimalarials and oral gold had relatively low toxicity rates.[13] Another meta-analysis[14] considered that antimalarials and methotrexate had the best ratio of toxicity to efficacy.

Intramuscular gold has long been used for the treatment of rheumatoid arthritis and is often the standard against which the efficacy of other treatments is measured. Although it is still extensively prescribed, its toxicity and poor long-term efficacy has led to renewed debate over its place in antirheumatic therapy.[24,25] Oral gold is less toxic but is also much less effective. Early enthusiasm for penicillamine has also been somewhat curtailed by a high incidence of adverse effects. The antimalarials are less effective than most other DMARDs but as they are generally less toxic and better tolerated they may be preferred in patients with milder forms of disease. Although sulphasalazine was originally introduced for the treatment of rheumatoid arthritis, results of early studies were unfavourable and it subsequently found its main use in the treatment of inflammatory bowel disease. However, re-investigation many years later demonstrated its efficacy and is now often one of the DMARDs of first choice.[1,23] Immunosuppressants have also been used in rheumatoid arthritis but there are concerns over long-term toxicity. However, methotrexate can improve disease activity when given once weekly in low doses that are too small to produce systemic immunosuppression and when used in this manner adverse effects occur commonly but are usually mild. In a recent long-term study[26] almost two-thirds of patients were still taking methotrexate after 5 years. The risk of hepatotoxicity remains a concern, but many rheumatologists[1,19,20] consider methotrexate to be a first choice DMARD. Improvement generally begins earlier with methotrexate than with other DMARDs. Concomitant use of folic acid or folinic acid is recommended by some as this can reduce the toxicity of methotrexate without reducing efficacy,[27,28] but the timing of administration may be important. The use of other immunosuppressants is more debatable but azathioprine and cyclophosphamide are still used in some patients with severe disease who have failed to respond to other drugs, especially in those with extra-articular manifestations such as vasculitis. Cyclosporin has also been shown to be effective in rheumatoid arthritis but, because of concern over nephrotoxicity, it is considered that it is best reserved for refractory disease; the use of low-dose regimens may help to minimise adverse effects. The microemulsion formulation of cyclosporin possesses a more predictable and improved absorption profile compared with the conventional oral formulation, and may enable lower doses to be used for a good clinical response.[29]

The use of corticosteroids in rheumatoid arthritis is controversial. Although systemic corticosteroids can suppress the symptoms of the disease, their usefulness is limited by adverse effects. They are usually reserved for use in patients with severe rapidly progressing disease that has failed to respond to other antirheumatics or when there are severe extra-articular effects. Systemic corticosteroids have also been used temporarily to control disease activity during initiation of DMARDs. In spite of problems with the adverse effects of corticosteroids it has been suggested that, in line with current thinking on the earlier use of more aggressive therapy for the control of inflammation, early use of short-term corticosteroids might also be appropriate.[30] Although corticosteroids are associated with bone loss,[31] this appears to be dose-related[32] and, at low doses, the benefits of corticosteroid therapy on inflammation and mobility might result in a reduced loss of bone in patients with rheumatoid arthritis. There is some evidence[49] to suggest that the rate of joint destruction may be substantially reduced by corticosteroids in low doses (such as prednisolone 7.5 mg daily) in patients with moderate to severe rheumatoid arthritis of less than 2 years duration; the corticosteroid should be gradually discontinued after 2 to 4 years to avoid possible long-term adverse effects. It is imperative that reduction in joint destruction should be distinguished from mere symptomatic improvement, which, at low corticosteroid doses, lasts only for 6 to 12 months. Intra-articular injections of corticosteroids may be used when there are acute flares affecting one or a few individual joints but they should be given infrequently.

A wide range of other drugs has been tried in rheumatoid arthritis,[16,21,33,34] but for most there is little clearcut evidence of efficacy. Studies[35,36] indicate that minocycline can produce modest beneficial effects in patients with rheumatoid arthritis, but the clinical significance of these improvements has been questioned[37] and it remains to be determined what role, if any, minocycline would have in the management of rheumatoid arthritis. Testosterone has produced clinical improvement in male and postmenopausal female patients. Much research has been conducted into using immunomodulators and immunotherapy. Interferons have produced results similar to conventional DMARDs but the need for repeated injections is a drawback. Other drugs that have been tried[38-40] include amiprilose, leflunomide, mycophenolate mofetil, zileuton, oral desensitisation with collagen, and immunoglobulins. Interest in the possible role of cytokines in the pathogenesis of rheumatoid arthritis has led to studies of various inhibitors of TNF-α such as tumour necrosis factor antibodies (e.g. infliximab), soluble tumour necrosis factor receptor (etanercept), and tumour necrosis factor receptor fusion protein, as well as interleukin antagonists.[41,42] A CD4 antibody (IDEC-CE9.1) and matrix metalloprotease inhibitors have also been studied. Other methods of treatment that are under investigation include gene therapy and autologous bone marrow transplantation. A rheumatoid arthritis vaccine is also in clinical trials. Some studies suggest that addition of fish oils and/or evening primrose oil to standard antirheumatic therapy might help to reduce pain and joint swelling.

Findings that significant skeletal bone loss occurs early in the disease have raised the question of the need for general measures to prevent osteoporosis in patients with rheumatoid arthritis.[30] Some[30] consider the use of oestrogen therapy in postmenopausal women with rheumatoid arthritis to be appropriate but to date the overall effect of such treatment is unclear.[43-45] The use of bisphosphonates such as disodium pamidronate is being studied.[46]

The treatment of rheumatoid arthritis during pregnancy presents its own problems; the rational selection of suitable drugs has been discussed in a number of reviews.[47,48]

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Soft-tissue rheumatism. Soft-tissue rheumatism includes a number of conditions such as fibromyalgia (fibrositis, muscular rheumatism, myofascial pain), humeral epicondylitis (e.g. tennis or golfer's elbow), frozen shoulder, Tietze's syndrome, fascitis, tendinitis, tenosynovitis, bursitis (e.g. housemaid's knee), and sprains and strains. It has a variety of causes and may be associated with overuse, trauma, infection, or systemic inflammatory diseases. Inflamed or displaced tissue may impinge on nearby nerves and produce compression neuropathies such as carpal tunnel syndrome. Soft-tissue rheumatic conditions are usually benign and can remit spontaneously. The management of some of these conditions has been reviewed.[1-6,11] Most will respond to selective rest of the affected region and splinting where appropriate. Gentle exercise, massage, application of heat, cold, or rubefacients can also be of benefit. Many soft tissue lesions respond to local injection of a corticosteroid given with a local anaesthetic.[7] Short-term use of oral NSAIDs may help to relieve pain and reduce inflammation of soft-tissue trauma. Topical formulations of NSAIDs have been used but although they are more effective than placebo for pain relief their role, if any, is unclear. Capsaicin has also been tried as a topical analgesic.

Pyridoxine has been suggested as a treatment option for carpal tunnel syndrome but there is significant controversy surrounding its efficacy[8] and high doses of pyridoxine given for prolonged periods have been associated with sensory neuropathy. There have been anecdotal reports of beneficial responses of carpal tunnel syndrome to hormone replacement therapy.[9,10]

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Spondyloarthropathies. The spondyloarthropathies are a group of seronegative arthritides which include ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disorders (enteropathic arthritis), and arthritis associated with infection as in reactive arthritis (aseptic arthritis).

Ankylosing spondylitis is characterised by arthritis of the spine and sacroiliac joints and sometimes there is also asymmetrical peripheral involvement. Males under 40 years of age are predominantly affected. The aim of management of the disease is to reduce pain and stiffness and to prevent spine and joint deformity, which is accomplished using a combination of active physical therapy and drug therapy. Exercises are used to strengthen muscles and to maintain a good posture and range of movement in joints. NSAIDs are used to relieve pain and inflammation, thus allowing the exercises to be performed. Some patients may require concomitant treatment with other non-opioid analgesics such as paracetamol for additional pain control. Indomethacin has been considered by some to be the NSAID of choice, although individual patient tolerance and preference often dictate the final choice of drug. Misoprostol is sometimes administered with NSAIDs in an attempt to reduce gastro-intestinal adverse effects such as peptic ulceration and haemorrhage. Phenylbutazone is sometimes used when other drugs are unsuitable but it should be noted that the use of phenylbutazone in the UK has been limited to hospital rheumatology departments because of the risk of occasional serious adverse effects. Systemic corticosteroids are rarely indicated but intra-articular injections of corticosteroids may be beneficial when one or two peripheral joints are severely affected. Although NSAIDs reduce inflammation in ankylosing spondylitis they do not influence the progression of the disease. Sulphasalazine, which has proven efficacy in ankylosing spondylitis (mainly in patients with peripheral involvement), may help to control severe or refractory disease; the efficacy of other second-line or disease modifying antirheumatic drugs used in rheumatoid arthritis (see above) remains to be demonstrated.

Psoriatic arthritis (or psoriatic arthropathy) is an inflammatory seronegative arthritis occurring in patients with psoriasis. In some patients the spine may be involved when the condition may be indistinguishable from ankylosing spondylitis. Less frequently some patients have a form of symmetrical arthritis resembling rheumatoid arthritis (see above). The psoriasis (p.1075) and the arthritis usually require separate treatment. Treatment of the arthritis is initially as for ankylosing spondylitis with NSAIDs and physical therapy. If these methods fail treatment with a disease modifying antirheumatic drug should be instituted. Gold compounds have been tried. Immunosuppressants such as azathioprine or methotrexate may be useful for severe or progressive cases but potential liver toxicity may limit the long-term use of methotrexate in some patients. Sulphasalazine has also been tried in some patients. Chloroquine and hydroxychloroquine should be avoided since they may precipitate skin reactions (see p.428). Systemic corticosteroids have little or no place in the management of psoriatic arthritis.

Reactive arthritis is characterised by sterile synovitis following 1 to 4 weeks after an infection most commonly of the gastro-intestinal or genito-urinary tract. Extra-articular features involving the skin, eyes, or genito-urinary tract may or may not be present. Reactive arthritis is also a feature of Reiter's syndrome. Reactive arthritis is treated with physical therapy and NSAIDs and, if indicated, intra-articular injections of corticosteroids; the role of antibacterials is less certain (see under Bone and Joint Infections, p.117).

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Still's disease. Still's disease is characterised by a high fever, polyarthritis, and an evanescent pink macular rash that is most prominent during bouts of fever; patients are seronegative for rheumatoid factor. Onset is usually in children under 5 years of age, but can occur in adults. Treatment is usually with aspirin or other NSAIDs or corticosteroids.

The name Still's disease has been used rather inconsistently to describe some types of juvenile chronic arthritis (see above).

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Pain

Pain is not only associated with physical suffering or hurting but has an emotional or mental component, hence its definition by the International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.' The emotional as well as the physical aspects need to be considered during treatment.

Under normal circumstances pain is the result of stimulation of peripheral receptors which transmit impulses through pain pathways to the brain. Pain receptors or nociceptors are of two basic types: mechanoheat and polymodal receptors. Mechanoheat receptors have a high stimulation threshold and respond to intense or potentially damaging noxious stimuli. These receptors are associated with rapidly conducting thinly myelinated Aδ fibres and their stimulation produces rapid sharp localised pain that serves to activate withdrawal reflexes. The other type of receptors are referred to as polymodal nociceptors as they respond to mechanical, thermal, or chemical insults. These receptors are also activated by cellular components that are released following tissue damage. Their impulses are transmitted slowly along unmyelinated C type fibres and produce dull, aching, and poorly localised pain with a slower onset.

Nerve fibres from nociceptors terminate in the dorsal root of the spinal cord before transmission by ascending pathways to the brain. There have been many theories on the processing of pain signals at the spinal level but the 'gate theory' proposed by Melzack and Wall is one of the best known. This theory postulates that the transmission of impulses, arriving from different receptors, to the brain is modulated by a gate mechanism in the substantia gelatinosa. Stimulation of small fibres opens the gate and facilitates transmission whereas stimulation of large fibres, which normally carry non-painful sensory input can close the gate and inhibit transmission. Transmission also appears to be modulated by several other mechanisms which can influence the sensitivity of the gate. Inhibitory control over the gate is produced by descending fibres from the brain which in turn are influenced by input from all parts of the body and by input from the cortex so that cognitive processes such as past experience can influence the perception of pain. When output through the gate exceeds a critical level transmission to the brain occurs to produce withdrawal reflexes, autonomic responses, and the sensation of pain. Feedback from this response system acts further to modulate the gate control system.

Pain associated with tissue damage results in increased sensitivity of the sensory system so that pain can occur in the absence of a clear stimulus. There may be a reduction in the pain threshold (*allodynia*) resulting in an exaggerated response (*hyperalgesia*) or a prolonged effect (*hyperpathia*). The effect of stimulation of high threshold nociceptors is usually transient but inflammatory mediators such as bradykinin, histamine, serotonin, and prostaglandins produced in response to tissue damage can produce peripheral sensitisation so that these receptors respond to low intensity or innocuous stimuli. Due to this increased activity central sensitisation also occurs. Neurones in the dorsal horn undergo prolonged alterations in their response properties so that they respond to input from fibres which do not normally evoke pain such as low threshold Aβ fibres which are activated by tactile stimuli.

Pain is often classified as being acute or chronic in nature although some forms of pain regarded as being chronic may consist of intermittent attacks of pain followed by relatively long pain-free periods. **Acute pain** is associated with trauma or disease and usually has a well defined location, character, and timing. It is accompanied by symptoms of autonomic hyperactivity such as tachycardia, hypertension, sweating, and mydriasis. Pain lasting more than a few months is usually regarded as being **chronic pain** and generally presents a different clinical picture. It is not necessarily readily associated with trauma or disease and its localisation, character, and timing are more vague than with acute pain. Furthermore, as the autonomic nervous system adapts, the signs of autonomic hyperactivity associated with acute pain disappear. However, patients with chronic pain experience physical, psychological, social, and functional deterioration. These demoralising factors contribute towards exacerbation of pain and must be considered during its treatment.

From an aetiological perspective, pain may be considered as being psychogenic or as being associated with an underlying disease or trauma. Psychogenic pain may rarely be delusional (only responding to psychiatric treatment) or may be due to psychologically induced chronic physiological changes. Patients with the latter type of psychogenic pain may develop chronic illness behaviour patterns, tend to respond poorly to conventional analgesics, and need behavioural therapy.

Physiologically, pain may be divided into nociceptive pain and neurogenic pain. *Nociceptive pain* follows activation of nociceptors by noxious stimuli as described above but is not associated with injury to peripheral nerves or the CNS. It may be somatic or visceral in nature, depending on which peripheral receptors or nerves are involved. Somatic pain is usually well localised and may be described as deeply located, sharp or dull, nagging, stabbing, throbbing, or pressure-like. Visceral pain is generally less localised and more diffuse than somatic pain and may be referred to remote areas of the body. Depending on the structure involved it is variously described as deeply located, aching, nagging, cramping, or pressing and may be accompanied by nausea and vomiting. Nociceptive pain usually responds to treatment with conventional analgesics.

The terms *neurogenic* or *neuropathic pain* are often used interchangeably to describe pain resulting from damage or dysfunction of peripheral nerves/receptors or of the central nervous system. The term neurogenic pain covers sympathetically maintained pains including causalgia and reflex sympathetic dystrophy, and painful conditions such as postherpetic and trigeminal neuralgia, and diabetic neuropathy. Pain associated with central nervous tissue, such as in central post-stroke pain (the thalamic syndrome) is referred to as central pain. The clinical signs of neurogenic pain can vary greatly. Some of the more common features include heightened pain sensitivity and sensations of superficial burning or stabbing (lancinating) pain. The pain may be associated with areas of sensory deficit or some form of autonomic instability. Neurogenic pain responds poorly to conventional analgesics and can be difficult to treat.

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General management of pain. There are several approaches to the management of pain, and combining approaches can result in an additive or greatly enhanced effect.

Early treatment is important as unrelieved pain can have profound psychological effects on the patient, and acute pain that is poorly managed initially can degenerate into chronic pain, which may prove to be much more difficult to treat. It is important to assess and treat the mental and emotional aspects of the pain as well as its physical aspects. Although drug therapy is the mainstay of pain treatment the addition of psychological, behavioural, or physical methods can enhance analgesia.

The transmission of pain impulses to the brain can be inhibited at a number of levels. Pain may be managed at a peripheral level as in the use of ice packs or NSAIDs to inhibit local responses to trauma and prevent stimulation of nociceptors. Techniques such as nerve blocks or cryoanalgesia can be used to inhibit peripheral transmission of pain. Intervention of pain processing at the spinal level can be accomplished using stimulation techniques or spinal injections of opioids, local anaesthetics, or other drugs. Analgesics such as the opioids can alter central processing of pain impulses.

The WHO has devised a regimen for the use of analgesics in the treatment of chronic cancer pain and this has been used by some authorities as the basis for a graded clinical approach in the treatment of both acute and chronic pain. In the WHO regimen drugs are selected from an analgesic ladder which starts with the use of a non-opioid analgesic alone. If pain is not controlled a weak opioid may be added. If this is not effective the weak opioid is replaced by a strong opioid and the non-opioid analgesic may be withdrawn. Some pain, such as neurogenic pain, incident bone pain, and some forms of visceral pain, respond poorly or not at all to opioid analgesics given in tolerable doses and at each stage, the analgesic therapy may be supplemented by the use of co-analgesics or other pharmacological or nonpharmacological adjuvant treatment to enhance analgesia and limit side-effects. The WHO ladder is described in more detail under Cancer Pain (see below).

Other methods of pain control that may be tried either alone or in combination with analgesics include physical methods such as physiotherapy, nervous system stimulation methods, and surgery. Physiotherapy can be an important part of pain management and may include massage and the application of heat and cold in many forms.

A number of stimulation techniques exist for the management of pain of which acupuncture and transcutaneous electrical nerve stimulation (TENS) are the most widely used. The rationale behind the use of TENS, in which the peripheral nerves supplying the painful area are stimulated by applying a low-intensity, high frequency electrical current across the skin, lies in the 'gate theory' of pain (see Pain, above). It is suggested that stimulation of large rapidly conducting myelinated nerves which normally transmit low-threshold tactile input closes the gate to transmission of pain through the spinal column by slow conducting unmyelinated nerves. However, other mechanisms may also contribute to the effect of TENS. In acupuncture, stimulation is achieved by insertion of small needles into specific acupuncture points. Heat or a small electrical pulsed current is sometimes applied to the needles to enhance the effect. There is much conflicting data on its mode of action. It may in part be explained by the 'gate theory', but opioidergic mechanisms are also involved as endogenous opioid peptides are produced and its effects can be reversed with the antagonist naloxone.

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Analgesics and analgesic adjuvants. Described below are drugs or groups of drugs used in the treatment of pain, including non-opioid and opioid analgesics and some drugs used as adjuvant analgesics.

Non-opioid analgesics. Paracetamol and aspirin and other NSAIDs are the first choice for treating mild or moderate pain and are used in moderate or severe pain to potentiate the effects of opioids. They are suitable for use in acute or chronic pain. Aspirin and other NSAIDs are thought to act by inhibiting cyclo-oxygenase and preventing prostaglandin formation; it is uncertain how paracetamol acts. NSAIDs are particularly effective in bone pain of malignant origin and pain due to inflammation. Aspirin and paracetamol are of similar potency in most types of pain but paracetamol only has a weak anti-inflammatory effect. Dependence and tolerance are not a problem with non-opioid analgesics but as the dose is increased, their efficacy reaches a ceiling. Most NSAIDs have a greater analgesic effect than aspirin or paracetamol in single doses but it has not been established whether this is true when used repeatedly in chronic pain. Adverse effects can limit the use of non-opioid analgesics. Aspirin and other NSAIDs inhibit blood platelet function, adversely affect the gastro-intestinal tract, and can precipitate hypersensitivity reactions including asthma. Paracetamol does not have the haematological or gastro-intestinal adverse effects of aspirin but large doses can produce severe or sometimes fatal hepatotoxicity; patients with cachexia or those with existing liver disease may be more susceptible.

Weak opioid analgesics. Codeine is traditionally the weak opioid analgesic of choice; alternatives include dextropropoxyphene and dihydrocodeine. Weak opioids are often given with non-opioid analgesics for the treatment of moderate or moderate to severe opioid-sensitive pain. Combinations of codeine with paracetamol produce a small but significant increase in analgesia compared with paracetamol alone and might be appropriate for occasional pain relief, but the incidence of adverse effects increases with repeated use. Combinations of dextropropoxyphene with paracetamol are no more effective than paracetamol alone for acute pain; efficacy in chronic pain is unclear and adverse effects may become troublesome.

Strong opioid analgesics. Strong opioids are mainly used in the treatment of severe acute non-malignant pain and cancer pain (see below). Their use in chronic non-malignant pain is somewhat controversial because of fears of psychological dependence and respiratory depression. However, in practice such problems rarely occur and those fears should not prevent patients being given effective analgesic therapy. Respiratory depression induced by opioids is generally a short-lived phenomenon that usually occurs in opioid-naive patients and is antagonised by pain. Although physical dependence can occur with continued use of opioids, withdrawal symptoms may be avoided by gradually tapering doses when the opioid is discontinued. The risk of psychological dependence and addictive behaviour is low when opioids are used to treat pain. Strong opioids include full agonists such as morphine, diamorphine, hydromorphone, methadone, pethidine, oxycodone, levorphanol, fentanyl, and alfentanil; partial agonists such as buprenorphine; and mixed agonist-antagonists such as pentazocine, butorphanol, nalbuphine, and dezocine. However, the use of opioids in the latter two groups can be compromised by their propensity to precipitate withdrawal symptoms in opioid-dependent individuals.

Morphine is the strong opioid of choice. The oral route is the most desirable route of administration and is appropriate for the control of acute and chronic pain in many patients. Morphine is well absorbed when given orally and has a short half-life so that administration of an immediate-release oral preparation offers a flexible means of dosage titration. Once initial pain relief is achieved, administration of modified-release morphine tablets every 12 hours may be more convenient for maintenance of analgesia in chronic pain, but this does reduce dosage flexibility and extra doses of immediate-

release oral morphine may be required for breakthrough or incident bone pain. Other routes such as intramuscular or intravenous injection for emergency pain control or intermittent infusion for patient-controlled analgesia may be used. Alternative routes should also be used where there would be problems with oral administration as in patients with persistent vomiting or at risk of vomiting, or with dysphagia, malabsorption, delayed gastric emptying, or intestinal obstruction.

Occasionally an alternative to morphine may be useful. Methadone, levorphanol, or oxycodone have a longer duration of action than morphine, but it should be noted that methadone and levorphanol, which have long half-lives, may accumulate and therefore should not be used long term because of progressive CNS depression. A rapid onset of action is provided by pethidine, alfentanil, and fentanyl, and dextromoramide is useful if a short action is needed. Diamorphine may be preferred to morphine when the parenteral route has to be used because the volume of solution to be injected is less with diamorphine than with morphine.

Troublesome adverse effects of opioids include sedation, nausea, vomiting, constipation, and, most seriously, respiratory depression. Tolerance generally develops to all of these effects except constipation, which should be prevented by regular use of laxatives. If tolerance to the analgesic effects of a particular opioid necessitates a dose increase which produces unacceptable side-effects, then another opioid may be tried since cross-tolerance is not complete.

Antidepressants. Subantidepressant doses of tricyclic antidepressants are considered to be useful in chronic neurogenic pain of the burning, dysaesthetic type such as postherpetic neuralgia and diabetic neuropathy; shooting pain has also been reported to respond to tricyclics. The primary role of antidepressants in the management of chronic pain is for patients whose pain is refractory to conventional analgesics or for whom the adverse effects of treatment are intolerable. They may be used in addition to conventional analgesics, and are particularly useful in the treatment of cancer pain of mixed aetiology. There is little evidence for an analgesic effect of antidepressants in acute pain but musculoskeletal pain has sometimes responded to tricyclic antidepressants. Amitriptyline has also been found to be useful for the prophylaxis of various headaches including migraine (p.443). Amitriptyline is usually the tricyclic that is selected for the treatment of chronic neurogenic pain, but other tricyclics have also been tried; the tetracyclic antidepressant mianserin and the selective serotonin reuptake inhibitors, fluoxetine and paroxetine have also been used but there is no evidence that these newer antidepressants have greater analgesic efficacy than the tricyclics.

Antiepileptics have membrane-stabilising properties that have been found useful in the relief of neurogenic pain especially when there is a stabbing (lancinating) element, as in trigeminal neuralgia; there have also been reports of efficacy in the treatment of diabetic neuropathy and for migraine prophylaxis (p.443). Side-effects are a problem with antiepileptics. Carbamazepine appears to be the antiepileptic most frequently used for neurogenic pain. Other drugs with membrane stabilising properties have also been used. **Antiarrhythmics** such as mexiletine and flecainide are reputed to be more effective than antiepileptics in neurogenic pain, but must be used with extreme caution in patients with cardiac disorders. Intravenous administration of lignocaine is potentially dangerous but has been useful in a limited number of patients with chronic pain syndromes such as adiposis dolorosa (Dercum's disease), neuralgic disorders, and diabetic neuropathy.

Corticosteroids have produced improvement, often substantial, in neurogenic pain, including pain caused by nerve compression or infiltration and sympathetically maintained pain. They are also of use in patients with cancer to relieve headache caused by raised intracranial pressure and for refractory pain caused by bone metastases. Corticosteroids also have added benefits of increasing well-being and appetite. Dexamethasone, methylprednisolone, and prednisolone have been used for pain management, sometimes in the form of long-acting depot injections administered locally with or without a local anaesthetic. The exact mechanism of action of corticosteroids in analgesia is not clear but may involve relief of pressure on nervous tissue by reduction of inflammation and oedema.

The use of **antipsychotics**, such as the phenothiazines, as adjuvant analgesics is controversial and apart from methotrimeprazine there is little convincing evidence that they produce useful analgesia. Methotrimeprazine is sometimes used as an adjunct in palliative care for the management of pain and associated restlessness, distress, or vomiting.

Hydroxyzine provides additional analgesia when used with opioids and has a useful antiemetic effect; it has been used in postoperative pain and chronic cancer pain.

Caffeine has been used with the aim of enhancing the effects of non-opioid and opioid analgesics but is of debatable benefit. There are similar doubts about whether caffeine enhances the effect of ergotamine in the treatment of migraine (p.446). In addition to doubts about caffeine enhancing the analgesic effect, it can add to gastro-intestinal adverse effects and in large doses can itself cause headache.

Muscle relaxants. Benzodiazepines and other muscle relaxants such as baclofen or dantrolene are useful for relieving muscle spasm (p.1303) in acute pain or cancer pain. Baclofen has been reported to be effective in the treatment of rectal or vesical tenesmus and in neurogenic pain states. Spasmolytics such as hyoscine may be useful in conjunction with analgesics in the treatment of visceral cancer pain due to the distension of hollow organs.

Bone modulating drugs such as calcitonin and bisphosphonates may be useful in cancer pain arising from bone metastases (see below) but have a slow onset of action and are second choice to NSAIDs. Bisphosphonates may cause an initial transient increase in bone pain.

Miscellaneous drugs. Following the discovery that epidural or intrathecal injection of opioids can produce effective analgesia many other drugs have been tried by these routes, either alone or with opioids or local anaesthetics, but their role, if any, in the management of pain remains to be determined. Some of these drugs, such as clonidine and ketamine, also appear to have analgesic properties when given by other routes.

See below under Some Analgesic Techniques for discussions of the use of inhalational analgesics, nerve blocks, patient-controlled analgesia, and rubefacients and topical analgesics.

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Some analgesic techniques. INHALATIONAL ANALGESICS. Some inhalational anaesthetics are used in subanaesthetic doses for their analgesic effect.

Nitrous oxide with oxygen is used to provide analgesia and sedation during dental procedures. A mixture of nitrous oxide 50% v/v and oxygen 50% v/v can provide good analgesia without loss of consciousness and is suitable for self-administration. It is used for short procedures such as dressing changes,[1,2] for pain relief during childbirth,[3] in the management of postoperative pain,[1] as an aid to postoperative physiotherapy, and for acute pain in emergency situations such as in ambulances. Continuous inhalation of nitrous oxide–oxygen has been tried for periods longer than 24 hours in the management of pain in terminal cancer.[4] However, such a practice is not usually otherwise recommended[1] as it may result in megaloblastic bone-marrow changes. Isoflurane and enflurane are sometimes used alone in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures although some workers have been unable to confirm an analgesic effect with subanaesthetic doses.

Methoxyflurane at concentrations of 0.3 to 0.8% v/v has been used for analgesia in dentistry and childbirth but daily use is not recommended because of its nephrotoxic potential.

Trichloroethylene in concentrations of 0.35 to 0.5% v/v has been used in some countries to provide analgesia for obstetrics, emergency management of trauma, and other acutely painful procedures.

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NERVE BLOCKS. Nerve blocks produce analgesia by interrupting the nervous transmission of pain signals either by temporary inhibition of conduction or by destruction of the nerve. Nerve blocks may be used in the management of acute or chronic pain associated with a well defined anatomical site, especially when the pain is unresponsive to or not adequately controlled by conventional therapy. Nerve blocks are either used alone or with analgesics in an attempt to enhance analgesia and reduce side-effects. The route of administration and method employed depend on the site to be blocked but may include peripheral nerve block, autonomic nerve blocks such as sympathetic nerve blocks and coeliac plexus block, and central nerve blocks such as epidural (including caudal) and spinal block. Local anaesthetics are used when a temporary effect is required. For a longer duration more destructive blocks using neurolytic agents such as phenol or alcohol or freezing of the nerve (cryoanalgesia) may be used, but even with these, the effects may last no more than a few months. Furthermore, neurolytic solutions produce variable and non-selective neural damage with poor correlation between pain relief and histological damage and some consider the risk of complications to outweigh the benefits obtained.[1]

The use of nerve blocks in the management of cancer has declined following the refinement of the use of conventional analgesics. In light of the risks and limited duration of effect, some consider that the value of such techniques may be limited to patients with a life expectancy of 3 months or less[2] and the main benefit of nerve blocks in cancer is to produce maximum pain relief rapidly. However, others support the view that chemical and thermal neurolysis can provide long-term control of severe cancer pain without a substantial incidence of adverse effects.[3] Neurolytic blocks may be of particular value in cancer pain syndromes involving the viscera or the torso, but are rarely applicable in the management of extremity pain.[4] Neurogenic pain is rarely helped by somatic neural block and may even be aggravated,[1] but block of the splanchnic nerves or coeliac plexus with alcohol or phenol is reputed to be effective in relieving severe intractable pain caused by cancer of the pancreas, stomach, small intestine, gallbladder, or other abdominal viscera, especially when the cancer has not spread to the parietal peritoneum.[5] Similar neurolytic blocks preceded by a local anaesthetic have also been used in patients with severe intractable pain of chronic pancreatitis, postcholecystectomy syndrome, or other chronic abdominal visceral diseases unrelieved by medical or surgical therapy.

Central nerve blocks using local anaesthetics with or without opioids are used for the management of acute pain such as labour pain during childbirth and postoperative pain; they are also sometimes used for cancer pain.[1,6]

Sympathetic nerve blocks using repeated injections of local anaesthetics or neurolytic agents have been used for sympathetically maintained pain. Intravenous regional sympathetic block is an alternative when a single limb is involved;[1] guanethidine is one of the drugs that has been used.[7]

Injections of local anaesthetics with or without corticosteroids are often used for blocks of localised painful joints. Nerve blocks are also used to block localised

painful trigger areas[8] such as postoperative or post-traumatic neuroma formation and for focal muscle pain.

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PATIENT-CONTROLLED ANALGESIA. Patient-controlled analgesia involves the use of automated delivery systems that enable patients to administer doses of an analgesic to themselves on demand. Doses of opioids are usually given intravenously, their frequency being controlled by each patient within the safety limits of the delivery system.

Patient-controlled analgesia has proved popular with patients and nursing staff and has been used successfully by children as young as 5 years of age[1,2] and by the elderly.[3] It is useful for the control of pain from a variety of causes including postoperative pain.[4,5] Nitrous oxide in oxygen has a long history of effective use in patient-controlled analgesia during childbirth; patient-controlled opioid analgesia may not be suitable for such pain.[6]

The safety and efficacy of patient-controlled opioid analgesia largely depends on the availability of adequately trained staff and reliable pumps designed to minimise the possibility of programming errors or tampering by patients or visitors. There have been isolated reports of patients receiving very large doses through deliberate operation of the system by relatives,[7] electrical interference,[8] or incorrect use by the patient or staff.[9,10]

In the simplest type of patient-controlled analgesia the patient is able to self-administer a fixed bolus dose on demand; further doses are not then permitted until a pre-programmed lockout interval has expired. Bolus doses are adjusted to prevent overdosage but maintain analgesic blood concentrations. Variable-dose patient-controlled analgesia has also been tried in which the patient selects one of several doses, although this method offered no advantage over fixed-dose systems in one study.[11] Some devices allow the dose to be administered as a short infusion to reduce adverse effects associated with high peak concentrations of opioids. In another commonly used method, sometimes described as patient-augmented analgesia, the patient is given a continuous background infusion which is supplemented by self-administered bolus doses. However, with this method patients may receive more opioids without any improvement in analgesia;[12,13] they may also experience more adverse effects such as nausea and vomiting, respiratory depression, drowsiness, and pruritus,[13,14] although this may depend on the size of the dose used for the background infusion.[15] It remains to be seen if there is any advantage with the more sophisticated devices that can be programmed to adjust the background infusion according to the frequency of the bolus demands.

Many opioids have been tried for patient-controlled analgesia. Morphine or pethidine are the most commonly used opioids but oxymorphone or hydromorphone may be useful alternatives. Also consideration should be given to the risks from the accumulation of the pethidine metabolite, norpethidine. The agonist-antagonist nalbuphine may also be a useful alternative because of its ceiling effect on respiratory depression. The use of buprenorphine and methadone may be limited by their long half-lives, while the action of drugs such as fentanyl and its analogues may be too short.

Most experience has been with the intravenous route, but the intramuscular, subcutaneous, epidural, and intrathecal routes have also been used. Epidural or intrathecal administration may allow the use of smaller doses but the development of respiratory depression can be delayed when using the epidural route; a greater degree of patient monitoring may be required when using either of these routes.[16] Epidural administration of bupivacaine with an opioid analgesic such as fentanyl has been tried for use in patient-controlled analgesia, and may allow reduced opioid doses, although whether this confers any clinical benefit is questionable.[17]

Other routes are also being investigated.

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RUBEFACIENTS AND TOPICAL ANALGESICS. Rubefacients or counter-irritants can relieve superficial or deep-seated pain probably by producing counter stimulation, which according to the 'gate theory' of pain (see Pain, above) helps to inhibit the transmission of pain signals. Their topical application produces hyperaemia or irritation of the skin and they are used alone or as an adjunct to massage in the management of a variety of painful musculoskeletal conditions. Some are also traditionally used in preparations for the symptomatic relief of minor peripheral vascular disorders such as chilblains. Substances commonly used in rubefacient preparations include nicotinate and salicylate compounds, essential oils, capsicum, solutions of ammonia, camphor, and nonivamide. Capsaicin, which is one of the active ingredients of capsicum, is used alone as a topical analgesic in a range of painful conditions, including neurogenic pain and rheumatic disorders. It appears to produce its analgesic effect partly through depletion of substance P, one of the neurotransmitters in pain pathways.[1,2] The effect of capsaicin does not rely on vasodilatation in the skin and it is therefore not considered to be a traditional counter-irritant but has been included in rubefacient preparations for the relief of muscular and rheumatic pain.

Application of heat to the skin can also help to relieve pain and melted hard paraffin has been used in wax baths as an adjunct to physiotherapy for painful joints and sprains. Warm kaolin poultices have also been used as a means of applying heat for pain relief.

Some NSAIDs have been used topically in the treatment of soft-tissue injuries and inflammatory musculoskeletal conditions, although this route does not necessarily avoid the adverse effects of systemic treatment. There is some evidence[3] to suggest that topical NSAIDs might be more effective than placebo but without comparative studies against other forms of treatment some[4] consider that their therapeutic role is unclear.

Other agents used as topical analgesics include compounds such as ethyl chloride and the halogenated hydrocarbon propellants; their evaporation produces an intense cold that numbs the tissues.

Local anaesthetics are sometimes included in topical preparations used for the relief of painful skin and musculoskeletal disorders.

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Pain in infants and children. Pain has often been undertreated in infants and children because of fears of respiratory depression, cardiovascular collapse, depressed levels of consciousness, and addiction with potent analgesics. Assessment of pain is also a problem in children of all ages and it is not that long since it was widely believed that neonates were incapable of feeling pain.

Most **neonates** requiring analgesia and receiving respiratory support can be managed with an infusion of morphine, although the infusion rate may need to be adjusted before they are completely weaned from mechanical ventilation. In neonates who are breathing spontaneously there is a substantial risk of respiratory depression with powerful opioid analgesics. Morphine sulphate has been used in such neonates but should be limited to those under intensive care, as for example after major surgery. For mention of the provision of analgesia in neonates in intensive care see Intensive Care under Sedation, p.638. Fentanyl citrate and codeine phosphate have also been used in neonates. Experience with the newer partial opioid agonists such as buprenorphine, nalbuphine, and meptazinol is limited. Sucrose solutions have been shown to reduce physiologic and behavioural indicators of stress and pain in neonates undergoing painful procedures although there had been some doubt expressed over whether this indicates effective analgesia.

In **infants and children** opioids are still the mainstay of analgesia for moderate to severe pain and morphine is the standard against which the others are compared. Techniques of continuous intravenous infusion with or without initial loading doses have become popular for postoperative pain relief, but titration of the infusion rate is necessary to achieve a balance between analgesia and respiratory depression. Subcutaneous infusions of morphine have also been used, mostly for the relief of terminal cancer pain in children. Intramuscular injections can provide excellent analgesia but are painful and therefore probably only suitable for short-term use. Other opioid analgesics used in infants and children have included codeine, buprenorphine, fentanyl, meptazinol, nalbuphine, papaveretum, and pethidine. Patient-controlled analgesia using morphine has been tried in children (see above).

Morphine has been given to children by the epidural route; experience with the intrathecal route is more limited.

Other methods of opioid drug delivery of possible value in paediatric analgesia include transmucosal, nasal, and transdermal administration.

Lytic cocktails (see p.77) consisting of chlorpromazine, pethidine, and/or promethazine have been administered parenterally for sedation and analgesia in paediatric patients, but some authorities have recommended that alternatives should be considered.

Local anaesthetics do not have the side-effects associated with opioid analgesics and are of particular value in neonates and children. They are especially suitable for the management of acute pain in day-care situations. Single injections given by the epidural route are often used to provide analgesia during and after surgery. Continuous epidural infusions of local anaesthetics have also been used. However, simpler techniques such as wound infiltration or peripheral nerve blocks can also provide effective analgesia for some procedures and are free of the problems of lower limb weakness or urinary retention associated with caudal blocks. Surface anaesthesia provided by application of eutectic creams (see p.1296) containing lignocaine with prilocaine to intact skin may be sufficient for some minor painful procedures in children, although use in those under 1 year of age is not recommended.

Non-opioid analgesics are used in children, either alone for minor pain or as an adjunct to opioid analgesics in severe pain; they are often given by the rectal route. Paracetamol is frequently the drug first employed but it lacks any anti-inflammatory effect. The use of aspirin in children is greatly limited because of its association with Reye's syndrome. Other NSAIDs are useful for