A-Z of medicines research

abpi

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About the Author

Dr Stephen Bartlett, born in 1947, studied chemistry and pharmacology at the University of Oxford, receiving his DPhil in 1974. Following a period of research at the University of Sheffield, he joined Pharmacia Fine Chemicals in Uppsala, Sweden, in a marketing role. In 1984, after completing an MBA at IMD in Lausanne, he took up a position in the central marketing department of Sandoz Pharmaceuticals in Basel, Switzerland, as International Product Manager, responsible for an injectable immunological product. Between 1990 and 1992 he headed the oncology business unit of the company's Canadian affiliate in Montreal. Dr Bartlett returned to the United Kingdom and started his own business in medical communications in 1993. He has undertaken projects in areas including allergy, fungal diseases, vaccines, sleep disorders and osteoporosis, and was for three years a member of the core team developing a leading health website dealing with age-related issues.

The Association of the British Pharmaceutical Industry

The ABPI is the trade association bringing together companies operating in Britain producing prescription medicines in the United Kingdom and other organisations involved in pharmaceutical research and development and those with an interest in the pharmaceutical industry. The Association is committed to improving public knowledge about medicines and the benefits that they bring to the health of the nation.

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1. Foreword

In the five years since the last edition of the *A to Z of Medicines Research* appeared, there have been more dramatic changes in the amount and pace of pharmaceutical research. New biological insights and high throughput technologies have meant that the number of potential compounds that can be put forward for testing has grown exponentially.

However, medicines research is still a long and expensive process. It takes years of careful evaluation and a lot of human and financial resources to bring new medicines to the point where they can be prescribed to the people who need them. An average of ten to twelve years and as much as £550 million are needed to transform a working idea for a new medicine into a finished product. But for the industry to fund its research efforts and supply innovative modern therapies in the future, it has to rely on the commercial success of medicines already in use, and the existence of a receptive regulatory and market environment .

Britain has traditionally been at the forefront of international medicines research - only the USA has discovered and developed more medicines. The treatments discovered and developed in laboratories in the UK help to save lives, reduce suffering and improve the quality of life for millions of people all over the world. While some of the focus of the *A to Z of Medicines Research* is on research in this country, the global nature of pharmaceutical research is such that interesting and relevant research in other countries has been included, so that the information is more comprehensive than it was in the previous edition.

Medical care has undergone a total transformation in the past 60 years. New generations of therapies have been introduced that have revolutionised medicine, making once-feared diseases uncommon and allowing the treatment of conditions that were once unrecognised or untreatable. The pharmaceutical industry has made a major contribution to this trend, but the battle is unfinished, and we see the industry turning its attention to some of the toughest targets of unmet need - cancer, viral disease and Alzheimer's, among others. We will continue to build on the vital partnership between the industry, the NHS and academic science to find the medicines of tomorrow, and to bring them swiftly to patients.

The *A to Z of Medicines Research* is primarily concerned with the future, but each section contains a brief overview of current treatments. The author, Dr Stephen Bartlett, goes into some detail where it is necessary to understand how research will affect present and future treatment, but in terms which aim to be approachable for anyone with an interest in a particular disease area. In many cases, more detailed information is available from groups representing patients and their carers, and their contact details are also included.

This booklet can only be a summary of the most important areas of the research that is going on all over the world. The research we are doing today holds the promise of answers to many of mankind's universal problems of disease, infection and old age. Pharmaceutical research may not bring any miracle cures, but the *A to Z of Medicines Research* points the way towards a brighter future for patients both in this country and all over the world.

Dr Richard Barker
Director General

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The ABPI wishes to thank member companies and the numerous other helpful people for the information provided in the preparation of the *A to Z of Medicines Research* and for permission to use illustrations. The information contained in the *A to Z of Medicines Research* was assembled during 2006 and 2007. While every effort has been made to ensure the accuracy of the information, the complexity of pharmaceutical research means that not all potential medicines listed here will successfully complete their clinical trials. Readers should therefore note that their availability for eventual use is by no means certain. The author and the ABPI disclaim all responsibility for errors and omissions.

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2. Introduction

The primary purpose of the *A to Z* is to provide an accessible, easy-to-use survey of current research in the pharmaceutical industry operating in Great Britain and overseas. It is structured so as to be understandable to the non-specialist, and to act as a source of general information for everyone with a personal or professional interest in healthcare. It is not a scientific document, and no attempt is made to detail the many complex theories that underpin modern medical research: those parts that refer to the way medicines work are invariably over-simplified. The section entitled 'Medicines Research Today' and the glossary define some of the technical terms used and attempt to put British medicines research into perspective within the world scene.

Many factors determine the choice and direction of research, and the balance of projects today is shifting significantly from previous decades. While the 1960s focused on antibiotics, and the 1980s on research into the central nervous system, the 1990s on monoclonal antibodies and molecular biology, the early years of this century are likely to be shaped far more by the new science of genetics and the Human Genome Project. These will have a big impact on many diseases, especially those with a hereditary component.

The issue of investment by the pharmaceutical industry is not addressed in detail. However, a summary is provided on trends in research expenditure. This is supplemented by recent data provided by the biotechnology sector and the larger UK-based pharmaceutical companies. It is difficult to determine the level of research expenditure in Britain by the international companies who operate here. It often cannot accurately be identified from the world-wide data available, but is undoubtedly significant.

Brief reference is made to Government and charity-supported research. The relationship between the pharmaceutical industry, academic, and NHS based research teams has continued to strengthen and remains an essential element in the fight against disease.

Inevitably, this booklet cannot be more than a snapshot of what is going on, because research and investment priorities are constantly changing. In particular, the reader should be aware that, through lack of space, there are many areas of ongoing work that have not been included in the fourth edition. These days, the internet is a prime source of information, and readers are advised to use it to explore the status of candidate medicines mentioned in the *A to Z of Medicines Research*.

3

Medicines Research Today

Britain's role in a global enterprise

The past 55 years have seen a revolution in our understanding of many diseases and their treatments. It has been a period in which:

- the structure of DNA was worked out, opening the way for a detailed understanding of inherited diseases and their treatment
- transplantation became a practical alternative for treating end-stage organ failure
- interferon, the first of a family of naturally occurring molecules called *cytokines*, was isolated, named and introduced for therapeutic use
- advanced scanning techniques were developed that have transformed the diagnosis and understanding of many human diseases
- monoclonal antibodies were discovered, enabling highly specific targeting of medicines and providing new types of medication for many diseases
- techniques for *in vitro* fertilisation were developed, bringing hope to many childless couples
- smallpox, a centuries-old scourge of mankind, was eradicated from the planet
- AIDS emerged, and with it the discovery of a family of human viral pathogens called retroviruses, of which HIV is one, leading to entirely new medicines to contain it
- the first gene therapy procedure was carried out, opening the way to treating serious inherited diseases
- the human genome was sequenced, laying the foundations in the coming decades for the development of many treatments for major diseases.

During this time, there has been a revolution in the number, specificity and safety of human medicines. Britain has played an important role in this process, and is recognised as a leader in medical and medicines research, with a proven record of high ethical standards and valuable skills in innovation. Many European, Japanese and American owned pharmaceutical companies fund major research groups here and research carried out in British laboratories and clinics lies at the heart of many of today's major medicines. About a fifth of the top 100 medicines in use today originated from research in this country - a record second only to that of the United States.

Britain hosts the headquarters of the European Medicines Agency (EMEA), the European Union's body for the licensing of new medicines, and has played a leading role in developing European regulatory activities. Medicines research has, however, become a truly global enterprise and this favourable situation will not be maintained without significant changes to strengthen Britain's appeal.

Until now, the UK has had particular strengths in preclinical research, pharmacology and early clinical pharmacology, but this position may be gradually eroding. The decline in skills among young people training for careers in science has a serious effect on the development of a knowledge-based industry. Apart from developing a more science-focused education system, there is a need for improved tax incentives and better regulation, so that pharmaceutical companies can enjoy a business environment where research can flourish.

The UK Clinical Research Collaboration (**www.ukcrc.org**) was established in 2004. It is a partnership between industry, government, professional bodies, the health service and research-funding medical charities that support clinical research in the UK. This initiative can be seen as a recognition of the need to strengthen the funding, co-ordination and execution of both academic and clinical research in this country, to ensure that Britain remains an attractive venue for medicines research.

Clinical trials have always been a vital part of the medicine development process, as they provide data on the best ways of treating diseases. Britain has made a significant contribution to this, and continues to do so. With a high concentration of research-based pharmaceutical and biotechnology companies, leading centres of academic medicine, and a long history of pioneering research, Britain is the leading venue in Europe for running the complex and often multinational studies needed to develop new medicines.

As well as providing new medicines for many diseases, as highlighted in this booklet, the pharmaceutical industry makes a substantial contribution to the British economy, providing income, employment and major investment. Earnings from the exports of medicines exceeded imports by £4.3 billion in 2006 and the industry has been a net earner for Britain throughout all of the past 30 years. The industry invested £3.3 billion in UK research and development in 2006 and employs more than 65,000 people, including 20,000 highly-trained scientists and doctors. In addition, the industry generates another 250,000 jobs in related industries. The pharmaceutical industry carries out more research by far than any other industry sector in the UK, bringing major health benefits to patients in Britain and all over the world.

Table 1. Time line of some major events in medicines research and use 1952 - 2006

1952	• *Salk polio vaccine developed (US)*
1953	• ***DNA Double helix*** *discovered by Watson & Crick*
1954	• *First successful* ***kidney transplantation*** *in USA*
1955	• *First* **oral treatment** *for diabetes introduced (Germany)*
1957	• ***Interferon*** *first isolated and named by Isaacs & Lindenman at NIMR, London* • **Imipramine** shown to be effective in depression • **Halothane** (ICI/Zeneca) anaesthetic gas introduced
1959	• First **semi-synthetic penicillin** marketed
1960	• **Methicillin** launched - active against many resistant bacteria • **Metronidazole** (Rhône-Poulenc) for parasitic and anaerobic bacterial infections
1961	• **Allopurinol** (Wellcome) developed for gout and arthritis
1962	• 1961-3 first **benzodiazepines** (Roche) for depression • First oral contraceptive launched - **Anovlar** (Schering Health Care) • **Azathioprine** (Wellcome) patented for immuno-suppression
1963	• **Ampicillin** (Beecham) major antibiotic discovered
1964	• **Ibuprofen/Flurbiprofen** (Boots) for arthritis and inflammation
1965	• **Propranolol** (ICI/Zeneca) a beta-blocker for heart disease
1967	• **Becotide** (Allen & Hanburys) for asthma • *First* ***heart transplant*** *by Christiaan Barnard in South Africa*
1968	• **Sodium cromoglycate** (Fisons) breakthrough in asthma
1969	• **Salbutamol** (Glaxo) introduced for asthma
1970	• **Levodopa (L-dopa)** a major advance in Parkinson's
1971	• *Mechanism of action of* ***Aspirin*** *discovered by Sir John Vane*
1972	• *Hounsfield develops X-ray computed tomography (CAT-scanning)*
1973	• **Tamoxifen** (ICI) introduced for hormone-dependent tumours
1975	• ***Monoclonal antibodies*** *discovered by Kohler and Milstein (UK)* • **Clozapine** (Sandoz) first atypical neuroleptic for schizophrenia enters clinical trial • **Clotrimazole** (Bayer) a major advance in treating fungal infections • **Nifedipine** (Bayer) for angina and hypertension
1976	• **Atenolol** (ICI) a beta-blocker introduced for various heart conditions • **Cyclosporin** (Sandoz) a major advance in transplantation • **Cimetidine** (SmithKline Beecham) launched for peptic ulcers
1977	• *Sanger and colleagues publish first sequence of a whole DNA genome (bacteriophage)*
1978	• *Birth of Louise Brown after Steptoe & Edwards develop In Vitro Fertilisation* • **Ranitidine** (Glaxo) anti-ulcer treatment discovered
1979	• ***Smallpox*** *eradicated from the world* • ***Interferon gene*** *first cloned*
1980	• *Discovery of Polymerase Chain Reaction (PCR) for amplifying DNA (US)*
1981	• **Captopril** (Bristol-Myers Squibb) first ACE inhibitor for high blood pressure
1982	• **Fluconazole** (Pfizer) - key advance in treating fungal infections
1983	• *Sir John Vane awarded Nobel Prize for work on* ***aspirin*** *and* ***prostaglandins*** • *Isolation of* ***HIV*** *as the cause of AIDS* • **Sumatriptan** (Glaxo) - major advance in migraine
1984	• **Cholestyramine** - trial shows lowering of cholesterol and coronary heart disease • Antibiotic **Augmentin** (Beecham) launched
1985	• **Acyclovir** (Wellcome) - major treatment for herpes launched
1986	• ACE inhibitor **Enalapril** (MSD) launched for high blood pressure • **Orthoclone** (Ortho) for transplantation - first licensed human monoclonal antibody
1987	• **Zidovudine** (Wellcome) - first AIDS treatment launched
1988	• **Lisinopril** (ICI/Zeneca) ACE inhibitor for hypertension and heart failure • *Nobel Prize awarded to* ***Sir James Black*** *for medicines discovery* • **Diclofenac** (Ciba-Geigy), an anti-inflammatory agent, launched • **Erythropoietin** (Janssen-Cilag), natural red blood cell stimulator, launched in the UK
1989	• **Omeprazole** (Astra) launched for gastric ulcers • **Simvastatin** (MSD) launched for lowering blood lipids • **Fluoxetine** (Eli Lilly) launched for depression
1990	• ***COX-2,*** *a major new target for anti-inflammatory drugs, discovered by scientists at Searle* • *First* ***gene therapy*** *experiment in a person with adenosine deaminase deficiency*
1991	• **Filgrastim** (Amgen) white blood-cell stimulant, G-CSF launched in UK • Inhaled form of steroid **Beclometasone** (3M Health Care) licensed for use in asthma
1992	• **Etidronate** (Procter & Gamble). First bisphosphonate in UK for osteoporosis

1993	• Specific monoamine oxidase-B inhibitor **Selegiline** (Orion) approved for Parkinson's disease • **Acarbose** (Bayer) first alpha glucosidase inhibitor for type 2 diabetes • **Paclitaxel** (Bristol-Myers Squibb) approved in UK for treatment of ovarian cancer
1994	• Dual serotonin and noradrenaline reuptake inhibitor **Venlafaxine** (Wyeth) approved for depression • Selective H2-receptor blocker **Ranitidine** (GlaxoWellcome) licensed for relief of acid indigestion
1995	• **Lamotrigine** (Wellcome) - major advance launched as monotherapy in epilepsy treatment • **Interferon beta-1b** (Schering Health Care) - first treatment for multiple sclerosis
1996	• **Olanzapine** (Eli Lilly) introduced for schizophrenia • **Losartan** (MSD) first angiotensin 2 receptor antagonist for high blood pressure • **Ropinirole** (SmithKline Beecham) launched for Parkinson's disease • **Saquinavir** (Roche) launched - first protease inhibitor for AIDS in UK
1997	• **Malarone** (Glaxo Wellcome) a new treatment for *P. falciparum* malaria is introduced • First medicines for Alzheimer's disease available - **Donepezil** (Pfizer) and **Tacrine** (Parke-Davis) • **Latanoprost** (Pharmacia & Upjohn) first prostaglandin analogue for glaucoma • **Reboxetine** (Pharmacia & Upjohn) first noradrenaline reuptake inhibitor for depression
1998	• **Viagra** (Pfizer) first treatment for erectile dysfunction • *UK Prospective Diabetes Study results published with important consequences for disease management* • **Rituximab** (Roche) launched for rheumatoid arthritis • **Montelukast** (MSD), a new class of inhaled medication, authorised for asthma
1999	• **Bicalutamide** (Zeneca) launched for prostate cancer • *Meningitis vaccination programme initiated* • **Zanamivir** (Glaxo Wellcome) first neuraminidase inhibitor for treating influenza launched in the UK • **Oxaliplatin** (Sanofi-Synthélabo) introduced for metastatic colorectal cancer
2000	• **Herceptin** (Roche) approved for breast cancer • New class of oral anti-diabetic agents introduced - **Rosiglitazone** (GSK) and **Pioglitazone** (Takeda) • **Bupropion** (GSK) launched for smoking cessation
2001	• **Sequencing of human genome reported to have been completed** • *Sir Paul Nurse and Dr Tim Hunt (UK) awarded Nobel Prize together with Dr Leland Hartwell (US) for research on cell cycle regulation of major relevance to the development of new cancer therapies* • **Caspofungin** (MSD) - first of new class of antifungal agents approved • **Glivec** (Novartis) a major advance in treating chronic myeloid leukaemia introduced • **Linezolid** (Pharmacia) - first entirely new class of antibiotic in 30 years
2002	• **Tiotropium** (Boehringer) first long-acting anti-muscarinic agent for treating COPD launched • First vaccine to protect against chickenpox **Varilrix** (GSK) introduced • **Xigris** (Eli Lilly) treatment for life-threatening sepsis made available • **Insulin glargine** (Aventis) first long-acting insulin analogue for diabetes launched
2003	• First fusion-inhibitor **Fuzeon** (Roche) for antiretroviral-resistant HIV infections introduced • **Ezetimibe** (MSD/Schering-Plough), a new type of cholesterol-lowering agent, launched in the UK • Recombinant PTH **teriparatide** (Eli Lilly) launched for treating post-menopausal osteoporosis
2004	• First medical treatment for stress incontinence in women, **Duloxetine** (Eli Lilly/Boehringer) • Introduction of **Bortezomib** (Janssen-Cilag) for treating multiple myeloma • Approval of the angiotensin receptor blocker **Candesartan** (Astra-Zeneca) and aldosterone antagonist **Eplerenone** (Pfizer) improves prospects for the treatment of heart failure • Monoclonal antibody **Efalizumab** (Serono) launched for treatment of moderate-to-severe chronic plaque psoriasis
2005	• **Erlotinib** (Roche) new oral treatment for advanced or metastatic lung cancer launched • Anti-IgE monoclonal antibody **Xolair** (Novartis) introduced for asthma treatment • First treatment **Rivastigmine** (Novartis) for dementia in Parkinson's disease introduced • Approval of two new monoclonal antibodies - **Cetuximab** (Merck) and **Bevacizumab** (Roche) improves survival prospects for patients with metastatic colorectal cancer
2006	• New type of antibiotic **Tigecycline** (Wyeth) approved for complicated skin and abdominal infections • Anti-TNF-α monoclonal antibody **Infliximab** (Schering-Plough) introduced as first biological agent for severe, treatment-resistant ulcerative colitis, following earlier approval in Crohn's disease • First inhaled insulin **Exubera** (Pfizer) approved for diabetes • **Rotarix** (GSK) launched as first vaccine to protect infants against gastroenteritis due to rotavirus

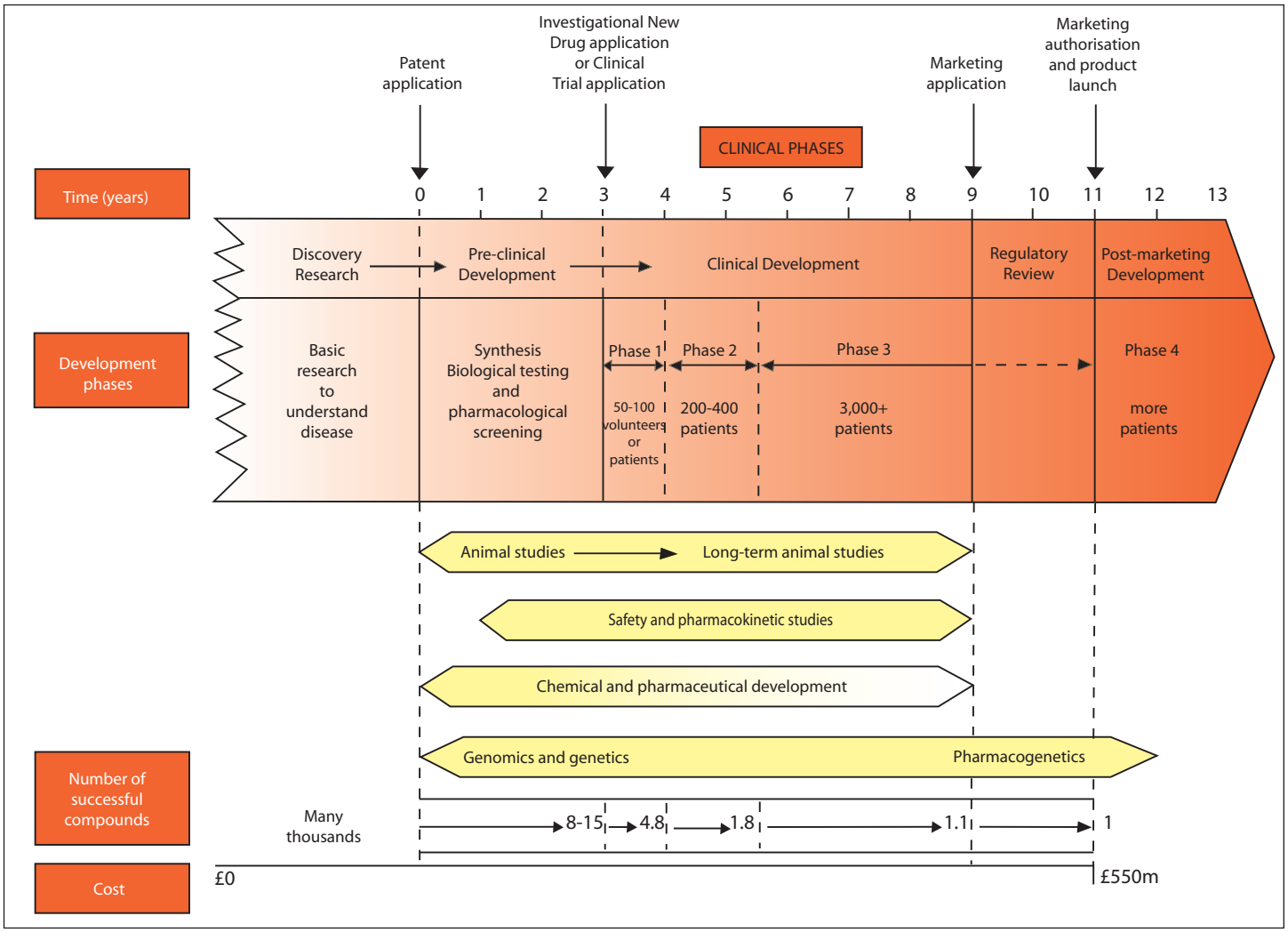


Figure 1: **Stages in the discovery and development of a new medicine**

The stages in the medicines research and development process

Throughout the *A to Z*, the terms *discovery research, development* and *Phase 1, 2, or 3 clinical trials* are used. It is important to understand these terms, so as not to be misled into believing that progress is more advanced than it really is. The time it takes to develop a new medicine is surprisingly long - on average around 10-12 years - and each stage must be passed successfully before the medicine can be approved for human use. The main stages involved in developing a conventional medicine are described below. Procedures for biological products (cytokines, growth factors, gene therapy, etc) differ in a number of respects and are covered by their own requirements and regulations.

Discovery research. This relates to the preclinical activities of chemists, biologists and pharmacologists who originate and test new active substances. Historically, new medicines have been sought from among compounds occurring naturally in plants, fungi or marine organisms, and this still happens today. When a biological activity is discovered in this way, the molecule causing it is extracted from its natural source, identified and synthesised - usually chemically. Chemists then make many close variations (called *analogues*), to try and maximise the desired effects and minimise unwanted effects.

The natural world continues to be a source of new medicines, but researchers have also developed many other sophisticated ways of creating new active substances. Increasingly, genomics, proteomics and synthetic chemistry are used in their design. These build on knowledge gained from the study of genes (*genomics*), a deeper understanding of disease processes, the study of the numerous protein products of specific genes (*proteomics*) and from the use of computer-aided design. The development of completely new classes of medicines typically depends on basic research into the fundamental mechanisms of disease and often involves collaboration with universities and other research institutes.

Traditional methods have been supplemented by new automated techniques such as *combinatorial chemistry* and *high-throughput screening* that have greatly speeded up the generation and testing of potential new medicines, allowing companies to examine hundreds of thousands of new molecules in the course of a year. Once a suitable 'candidate' compound has been identified, it enters the development stage.

3

Preclinical development. Much work has to be done to determine whether a potential new medicine is acceptably safe and sufficiently stable before it can be given to humans. Pharmacology (the science of how medicines act in the body) is vital at this early stage, and preclinical investigations concentrate on the formulation of the medicine - whether it is prepared as tablets, injections or sprays, etc - and on optimising the active ingredient - for example, to improve its solubility. Attention is also paid to how the new medicine will be delivered to the part of the body it is designed to act on, and how it is metabolised (broken down) by the body. Even small changes in the active molecule can make big differences to how it behaves in the body, as can changes in its formulation and method of delivery. Incremental innovation in an existing medicine can improve its effectiveness and alter its side-effect profile, or make it easier to take. These changes are not just 'me-too' medicine, but deliver real clinical benefit.

Early on, pharmacological scientists also have to establish a *proof of principle* - to show how the new medicine works - and to find out how it is likely to be absorbed and excreted by the body. In parallel with this, a large-scale manufacturing process must be worked out, enabling it to be made in sufficient quantity for large-scale clinical testing and eventual use in patients.

Translational medicine is an important aspect of the early development process, and Britain has an acknowledged competence in this field. Narrowly defined, the term refers to the skill of transferring research effectively from preclinical (animal) models to early clinical research in man. More recently, the term has been used to cover medicines development overall, and describes the process connecting basic research with clinical application of medicines research.

Turning a scientific theory into a new medicine takes around 10-12 years. During this time, computer models of new molecules will be studied, thousands of variations will be investigated in the test tube and a small number of promising compounds will eventually go on to be studied in animals. Animal research is essential to help scientists evaluate the safety and effectiveness of new medicines, providing guidance to enable researchers to bridge the gap between the test tube and the patient. The use of animals in research is carried out under strict legislative controls. Only when doctors and scientists are confident that they can do so without undue risks will the potential new medicine be studied in people.

Before a new medicine may be given to humans in the UK, an application has to be made to an agency of the Department of Health known as the Medicines and Healthcare products Regulatory Agency (MHRA) for a certificate to conduct clinical trials. The equivalent application in the United States is known as an Investigational New Drug (IND) application and is made to the Federal Drug Administration. In the European Union, it is known as an Investigational Medicinal Product (IMP). The application is reviewed by independent medical and scientific experts, who make their recommendation on whether the trial can start, or whether more information is required. If a certificate is granted, a new medicine will pass through a long and complex process of clinical studies before the company can seek marketing authorisation for its sale and widespread use. The conduct and management of clinical trials in the UK is governed by European Union legislation, which sets standards known collectively as Good Clinical Practice (GCP).

Clinical development Clinical trials for registration purposes are conventionally divided into three phases, although companies may sometimes combine two of the three phases (1 + 2 or 2 + 3).

Phase 1 trials are the first time the new substance is administered to humans, usually in studies of healthy, informed volunteers conducted under the close supervision of a qualified doctor. The usual purpose of Phase 1 trials is to determine if the new compound is tolerated and whether it behaves in the human body as predicted by the previous experimental investigations. Starting doses will be the lowest possible consistent with obtaining this information, but may gradually be raised to the expected therapeutic dose level. A new type of Phase 1 study uses a technique known as micro-dosing. This makes use of amounts of active substance too small to have a therapeutic effect, but that quickly provide sufficient information about its action in the body to decide whether it is worth continuing the compound's development.

If the compound under investigation is particularly powerful, as in cancer treatments, for example, it may be that people who actually have the condition will take part in the trials. Nevertheless, it is important to be clear that Phase 1 trials are generally ***not*** designed to test whether a substance is effective in treating disease and even where patients are used instead of healthy volunteers, the trials are essentially non-therapeutic.

Phase 2 trials are the first stage at which the medicine is given with the intention of treating an illness. Different doses are given to establish whether the compound is tolerated as well as in healthy volunteers, to see if it affects the disease or its symptoms, and to identify a suitable dose for large-scale (Phase 3) studies. Patient numbers in Phase 2 trials are usually limited.

Phase 2 studies are often divided into Phase 2a (short-term, in limited patient numbers) and Phase 2b (larger, longer and more focused on efficacy), and there may be modifications to product formulation and/or dosing schedules between the two. In addition, long-term animal toxicity testing and some other more specialised clinical trials, such as studies of the effect of food intake or in special populations (e.g. elderly patients) will often take place in parallel during Phase 2. It is usual for the formulation of the active substance to be finalised before Phase 2b studies begin, but laboratory testing, such as product storage stability testing, will also be carried out during Phases 2 and 3.

Phase 3 trials only follow if there are encouraging results in the Phase 2 studies. In such trials, the new medicine is compared with a dummy medication, called a *placebo*, or with another medicine already used for the disease under investigation, to provide a reference standard. Patients are allocated randomly to one of the groups and during the trial neither the doctor nor the patient knows which preparation is being given. Such a trial is termed a *double-blind, randomised, controlled trial* and is regarded as the type of trial that is most likely to give a clear, unbiased result. When the code is broken, a positive result would be indicated by an improvement in those patients who received the real medication as compared with those on placebo or the other active treatment. Phase 3 trials usually involve much larger numbers of patients (hundreds, or more likely thousands) than Phase 2 trial, to enable precise statistical evaluation of the results. If the medicine proves successful and well tolerated at this stage, the way is open for an application for a marketing authorisation (MAA in Europe,

NDA in the United States) to be made. This includes all the data generated on the new medicine and runs to many volumes.

Clinical study of a compound does not cease once it has been approved for use. So-called **Phase 4** trials are performed to develop a better understanding of:

- how well it works in a broader patient population
- its long-term benefits and the very rare risks that cannot be picked up in earlier clinical studies, because of the smaller numbers involved
- the most effective ways to use it.

Phase 4 trials, which often take place in a general practice setting, are subject to strict rules governing how they are carried out, as with all clinical studies in the UK. They are designed to answer significant clinical questions that have not been addressed by earlier studies. Safety is a key focus of Phase 4 trials, which tend to be conducted in much larger numbers of patients. They may also yield important data on the economic aspects of medicine use.

Pre-approval clinical studies account for a large, and increasing, proportion of the cost of developing a new medicine. Each successive clinical stage tends to be more expensive than the previous one (Figure 2). Out of 10-15 compounds entering Phase 1 studies, only one is likely to survive through to licensing.

The time scales needed for clinical studies are very variable. For example, if a new compound is an antibiotic for treating urinary tract infections, a positive result will be apparent in each patient within a few days as the infection is eradicated. However, in chronic diseases, such as multiple sclerosis, AIDS, Alzheimer's, arthritis, cardiovascular disease, or some forms of cancer, a trial may last a year or more in each patient and involve long-term follow-up to verify that clinical benefits persist over time.

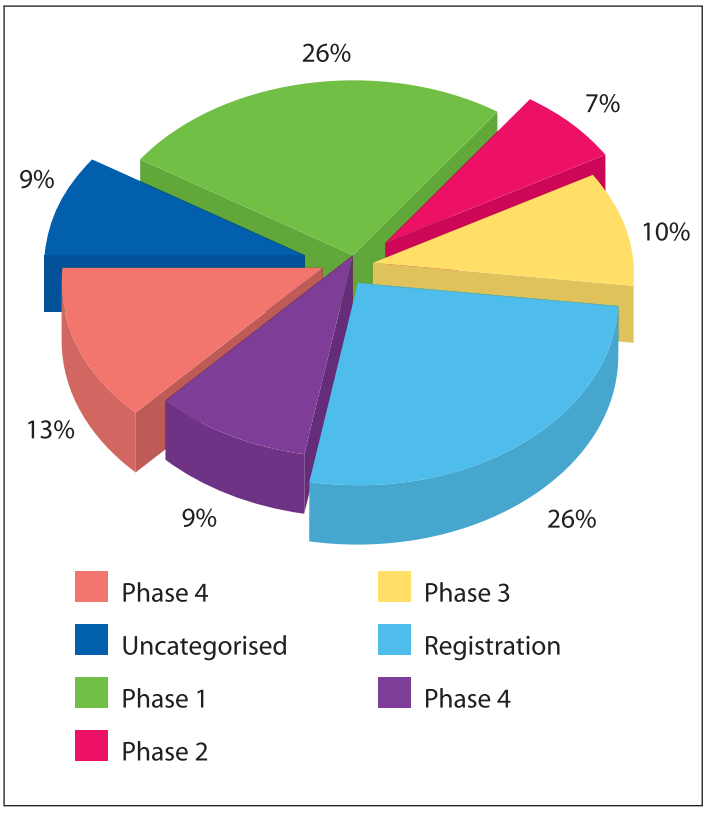


Figure 2: **R&D costs of new medicines development in the US by phase in 2004**
Source: PhRMA annual membership survey 2006

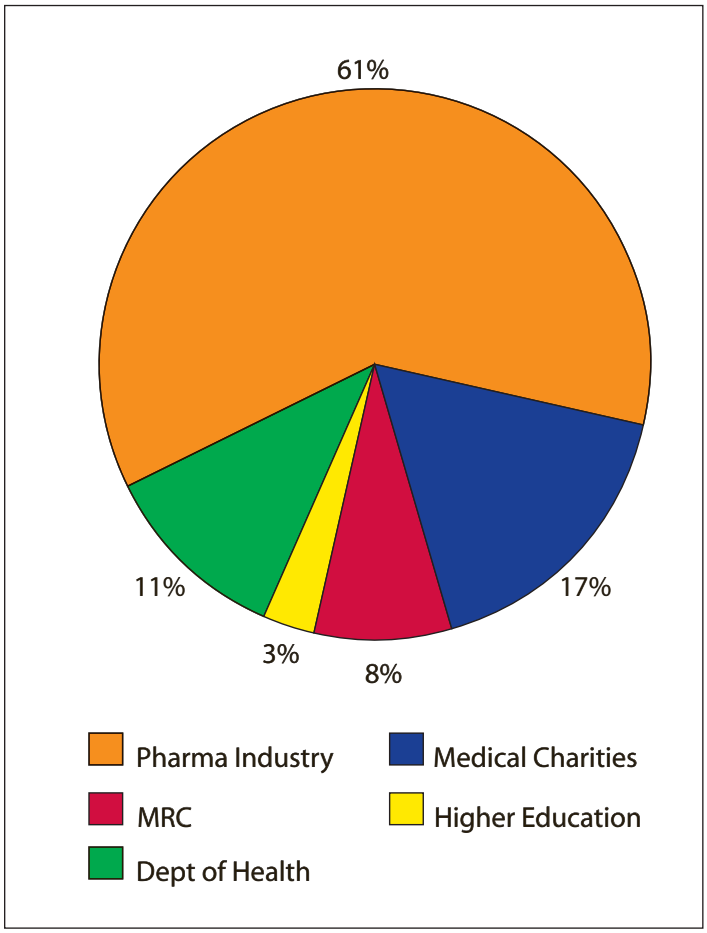


Figure 3: **Funding of healthcare-related R&D in the UK by the pharmaceutical industry, medical charities (including the Wellcome Trust) and government in 2004/05**

Despite these complexities, the number of entirely new medicines reaching the British public has remained fairly steady for the last ten years at around 25 a year, with the time from discovery to launch averaging 10-12 years over this period.

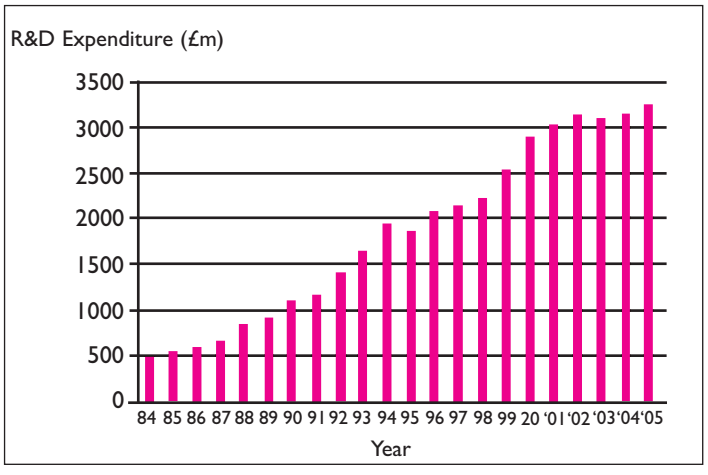


Figure 4: **Total R&D investment in the UK by the pharmaceutical industry**
Source: ONS Survey: Research and Development in UK Businesses

2004/05 R&D SPEND (£millions)	
GlaxoSmithKline	**£2,839.0**
AstraZeneca	**£1,980.8**
Pfizer	£597.8
Biotech sector (top 10) [Majority British owned]	£275.4
Eli Lilly	£147.5
Shire	**£112.5**
Roche	£101.0
Merck Sharp & Dohme	£62.4
Novartis	£56.4
Wyeth	£49.7
Janssen-Cilag	£35.7
Organon	£30.6
Skye	£27.9
Yamanouchi (now Astellas)	£24.9
Boehringer Ingelheim	£24.6
Bristol-Myers Squibb	£24.5
GRAND TOTAL	**£6,746.2**

Note: entries in **red** are global R&D spend, otherwise spend in UK only. Data from DTI "Research and Development Scoreboard".
Biotech Top 10 = Celltech, Cambridge Antibody Technology, Acambis, OSI Pharmaceuticals, Vernalis, Xenova, GW Pharmaceuticals, Prostrakan, Oxford Biomedica, Ark Therapeutics.

Table 2: **2004/05 R&D expenditure of top 10 biotechnology and top 15 pharmaceutical companies with a significant R&D presence in the UK**

Medical research investment in the UK

There are three main sources of medical R&D investment in the UK: industry, government and medical charities. (Figure 3) The pharmaceutical industry accounted for more than 60 per cent of this R&D investment during 2004/05.

R&D investment by the pharmaceutical industry

Industry investment has grown steadily over time, and especially so in the past two decades. Annual surveys by the Office of National Statistics show that total R&D expenditure by the industry in the UK, including capital investment, has risen from £475 million in 1984 to £3,308 million in 2005. Throughout this period, the annual increase in investment exceeded inflation in almost every year.

The R&D expenditure of selected major pharmaceutical companies with a research presence in the UK in 2004/05 is shown in Table 2. In addition, ten major biotech companies spent more than £275 million between them on research and development.

Many foreign-owned pharmaceutical companies have established dedicated discovery research facilities in the UK, including:

- Eisai Hatfield Research Laboratories
- Genzyme European Discovery Research Centre, Cambridge
- Merck Sharp & Dohme Neuroscience Research Centre, Harlow
- Novartis Institute for Medical Sciences, London
- Organon Research Centre, Newhouse
- Pfizer Global R&D European Headquarters, Sandwich
- sanofi-aventis Research Centre, Alnwick
- Servier Research & Development, Slough

In addition, many other companies carry out development work in Britain as part of their broader UK-based activities, including: Amgen, Bayer Schering, Boehringer Ingelheim, Ipsen, Leo, Merck Serono, Novo Nordisk, Otsuka, Pierre Fabre, Proctor & Gamble, Schering-Plough, Solvay, Dainippon-Sumitomo, Takeda and Wyeth.

The industry has invested substantial amounts in building R&D facilities in the United Kingdom. Capital investment projects typically span several years and levels of investment vary from year to year. However, some recent highlights include:

- GlaxoSmithKline (UK) has invested more than £150 million in capital projects to support its R&D efforts in the UK, including a £40 million centre for biomedical imaging attached to Hammersmith Hospital in London.
- Pfizer (USA) opened a £135 million Pharmaceutical Sciences building at its UK research centre. The laboratories at Sandwich in Kent, which discovered Viagra and the anti-fungal fluconazole, play an important role in the company's global research and are the largest biomedical R&D site in Europe.
- AstraZeneca (UK) opened a new £61 million cancer research facility. The company has also opened new large scale laboratories in Macclesfield, representing an investment of £24 million.
- Johnson & Johnson (USA) inaugurated a new building in High Wycombe for its R&D and diagnostics businesses.
- Abbott Laboratories (USA) has built a £39 million biotechnology facility at Dartford, Kent and is creating a centre of excellence for diabetes care at Witney, Oxfordshire.
- Roche (Switzerland) has opened a £75 million new UK headquarters, incorporating a 24-bed Clinical Pharmacology Unit.
- Merck Sharp & Dohme (USA) expects to complete work on a new global centre for chemistry in Hertfordshire as part of its investment in preclinical research.
- UCB (Belgium) is investing £14.5 million in new laboratories at the former Celltech R&D site in Slough.
- Eli Lilly (USA) has invested heavily in new technologies such as systems biology, genomic medicine and bioinformatics and recently opened new £25 million laboratories in Surrey.

R&D investment by government agencies and medical charities

The second major source of funds for medical research is central government, via the Medical Research Council (MRC), the Higher Education Funding Council for England (HEFCE) and the Department of Health (DH). In 2004/05 the MRC spent about £420 million funding research programmes in universities and MRC institutes and units, including training awards and fellowships. In addition, the Government allocated £140 million towards medical research through the HEFCE and a further £601 million for healthcare related research through the Department of Health (NHS research). It has recently been decided to combine MRC and NHS research spending, with the aim of strengthening and co-ordinating research efforts and ring-fencing the funding.

Charities are the third major contributors to medical research. In 2004/05, the major medical charities allocated nearly £400 million to medical research. In addition to charities that support research on a specific disease, the Wellcome Trust is a major provider of funds for biomedical research of all types, making some £480 million available to medical project funding and genetics research in the year to September 2005 (some outside the United Kingdom).

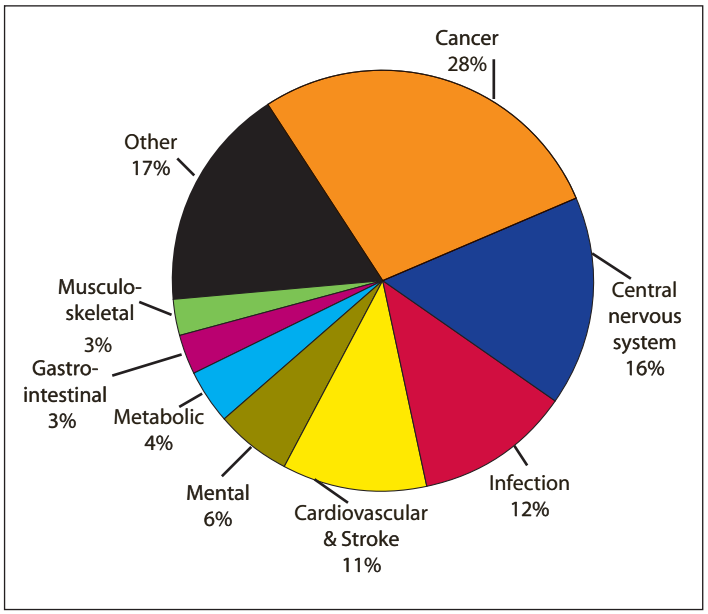


***Figure 5:* Disease-specific medical research expenditure in the UK in 2004/05 by eleven major non-profit UK organisations analysed by the UKCRC.**
Adapted from UKCRC report "UK Health Research Analysis"

The UK Clinical Research Collaboration (UKCRC) recently analysed UK research spending of eleven major government and charitable bodies that fund health research. Approximately £950 million was spent during the 2004/05 financial year by these bodies, of which 75 per cent could be linked with a specific disease, while 25 per cent was of a general nature. Of the disease-specific funding (Figure 5), the largest single share went to cancer research (28 per cent), followed by research on central nervous system disorders (16 per cent), infections (12 per cent) and cardiovascular disease, including stroke (11 per cent).

The UKCRC analysis also identified the breakdown of research spending by activity. This showed that only 16.6 per cent of this

The UKCRC Health Research Funding analysis focused on the following government and charity organisations:

- Department of Health (England)
- R&D Office, N. Ireland Health & Personal Social Services
- Chief Scientist Office, Scottish Executive
- Wales Office of R&D for Health and Social Care
- Medical Research Council
- Biotechnology and Biological Sciences Research Council
- Engineering and Physical Sciences Research Council
- Economic and Social Research Council
- The Wellcome Trust
- Cancer Research UK
- The British Heart Foundation

funding was related to the development or evaluation of therapeutic interventions, while fundamental research (aimed at understanding normal body functions and processes) and aetiological research (into the risks, causes and development of disease) each accounted for one third of total expenditure. More narrowly, research into the development and evaluation of pharmaceutical treatments of disease (the clinical trials with which this booklet is primarily concerned) represented only 6.8 per cent of the research spending of these eleven non-profit bodies (equivalent to about £65 million).

These charts illustrate the enormous financial contribution made by the pharmaceutical industry to the development of new treatments of disease. They also show the great importance of charitable giving - support that makes much basic medical research possible and paves the way for the discovery of new medicines.

The current research and development pipeline

One of the results of this substantial investment is the creation of a large pipeline of potential medicines under development, as shown by a survey conducted by the Association of the British Pharmaceutical Industry in 2006 (Table 3). This spans most major

Therapeutic area	NUMBER OF MEDICINES IN CLINICAL TRIAL IN			
	Phase I	Phase 2	Phase 3	Phase 4
Allergy	6	1	3	1
Antibacterials	9	5	12	4
Antifungals	-	3	2	1
Antivirals (incl. AIDS)	15	17	7	10
Bone metabolism	2	1	5	2
Cancer	68	62	40	20
Cardiovascular	35	44	30	15
Contraceptives	2	2	-	1
Dementia	7	12	1	2
Depression	9	8	6	4
Dermatologicals	6	6	6	6
Endocrine (incl. Diabetes)	24	16	19	8
Epilepsy	3	3	1	2
ENT, eyes	3	-	4	-
Gastrointestinal	8	14	16	5
Genito-urinary	9	11	3	9
Immunologicals	19	14	11	2
Lipid-regulating drugs	10	6	6	1
Musculoskeletal	14	15	8	5
Obesity	13	9	2	-
Obstetrics/Gynaecology	5	1	1	-
Pain	13	15	3	5
Parkinson's	5	5	3	5
Psychoses & related disorders	19	12	8	7
Respiratory (incl. Asthma, COPD)	21	27	5	7
Sleep disorders	2	4	4	3
Vaccines	15	17	11	6
Miscellaneous/other	20	19	23	6
TOTAL	**362**	**349**	**240**	**137**

Table 3: **Number of compounds in clinical trials arising from the R&D programmes of 47 companies operating in the UK.**
Source: ABPI Survey 2006

areas of human illness, with particular emphasis on cancer and diseases of the central nervous, cardiovascular, and respiratory systems, as well as gastro-intestinal disorders and infectious diseases, including the development of new vaccines.

All 47 companies have new medicines in clinical trials. From the information provided, there were some 950 compounds in pre-registration clinical development in 2006. 362 of these were in Phase 1, 349 in Phase 2 and 240 in Phase 3 - clearly a very healthy pipeline. This compares with 561 clinical development compounds from companies surveyed for the last edition of this booklet in 2001. Overall, the largest number of compounds are being developed for cancer (170), diseases of the cardiovascular system (109), mental disorders (62), diseases of the endocrine system (59), respiratory diseases (53), viral infections - including HIV/AIDS - (39), gastrointestinal diseases (38) and musculoskeletal diseases (37). In addition, 43 vaccine development projects and 44 projects to develop new immunological treatments were also in progress.

The companies surveyed also reported that they had 137 trials in progress at the Phase 4 (post-registration) stage. Such studies help to gain a better understanding of the safety profile of a new medicine in a wider population of patients and to refine knowledge of the best ways of using the medicine, which may eventually lead to new applications.

More about clinical trials

Doctors are increasingly adopting evidence-based treatment, formalised in the guidelines issued by the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN). This means using treatments whose effectiveness has been established objectively, through clinical trials. Clinical trials are therefore vital for establishing the best way to use medicines, as well as for providing the evidence of safety and efficacy required for regulatory approval. In view of their increasing importance, this section looks more closely at clinical trials and how they are performed.

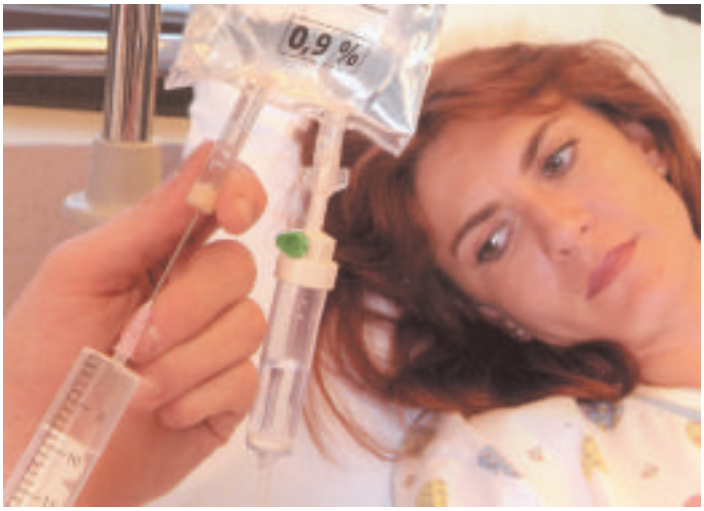
Types of clinical studies

There are a variety of different types of clinical studies and they are used for different purposes.

Cross-sectional studies (surveys) give information about a medical situation at a particular time - for example:

- How many people in the UK have diabetes?
- How does the degree of seriousness of rheumatoid arthritis affect a person's use of healthcare resources?

Longitudinal studies are used to show how a disease or treatment acts over time. They may be observational - as when a group of people who are initially disease-free are followed for a period of time to see how many develop a specific medical condition (this type of study is called a *cohort study*) - or they may involve giving a medical (or other) treatment and measuring the effect it has on the target disease (an *intervention study* or *intervention trial*). Study length can vary from a few days or weeks to decades, and the numbers of people involved may vary from a handful to many thousands, depending on the questions being studied.



Longitudinal studies are more demanding of participants, as they will involve several doctor/hospital visits at different times and examinations that may need to be repeated at intervals. Participants need, therefore, to make sure that they are willing and able to follow such a schedule. However, it is likely that at least some of these visits and examinations would have been required anyway as part of a patient's normal care.

Most clinical trials mentioned in this booklet are smaller and of shorter duration than these two studies, and are typically aimed at answering questions such as:

- Is medicine A more effective for treating disease X than medicine B?
- What is the best dose of medicine to give to this type of patient in this situation in order to provide the best balance between therapeutic effects and side effects?

One well-known example of a large ***cohort study*** is the Framingham study, carried out in the United States. More than 5,000 inhabitants of the Massachusetts town of Framingham were entered into this study from 1948 onwards and their health continues to be monitored even today. A second cohort, consisting of children (and their spouses) of the original study participants, was recruited in 1971, and a third cohort (children of children) are now being enrolled. The Framingham study has provided a great deal of information about the course of and risk factors for cardiovascular diseases.

The UK Prospective Diabetes Study was a major and influential ***intervention study***. This 20 year-long study also enrolled over 5,000 people. It demonstrated the health benefits of tight medical control of blood glucose level and blood pressure in people with diabetes. The findings of this study, published in 1998, provided important evidence on which the NICE guidelines for treating diabetes were based.

Such studies are required for regulatory approval of medicines, as well as for advancing medical practice, and it is important that they should be well designed and executed if the results are to be relied on.

Some studies examine the economic, as well as the medical, consequences of a treatment. These are known as *pharmacoeconomic studies* and are used to draw conclusions about the cost-effectiveness of different treatments. This may affect whether or not they are recommended for widespread use.

Who can participate in a clinical trial?

Who participates in a trial can have a marked effect on the results observed. For example, a medicine can have different effects and side-effects in elderly people than in young people, or may be more effective at one stage of a disease than another. Study results need, therefore, to be seen in the context of the group of people in which they were obtained, as they may not apply to others, and much thought is devoted to deciding which participants should be included in a study.

The selection of participants is carefully defined in advance, through the setting of *inclusion* and *exclusion criteria* which determine whether a person can take part in a trial. These vary greatly between trials, but usually concern aspects such as:

- disease severity (often, as defined by a specific set of tests)
- disease duration (newly diagnosed/over X months/fewer than Y years, etc)
- patient age (e.g. older than 18 years, less than 65 years, etc)
- patient body mass (body mass index less than/greater than X)
- existing use of other (possibly interfering) medicines
- pregnancy or breast-feeding
- known risk factors for a harmful reaction to study medicines
- presence/absence of specified medical conditions
- number of disease episodes per year (if a recurrent condition).

Clinical studies designed for registration purposes have, in the past, been criticised for being too restrictive. Children, pregnant women and those aged over 65 were often automatically excluded from many studies, and others, such as specific ethnic minority groups, may have been under-represented. This resulted in a lack of knowledge about whether/how these individuals could be treated with a given medicine. These shortcoming are now recognised, and increasingly, a broader group of patients is entered into trials to reflect the eventual users of the medicines.

Making sure clinical studies give reliable answers

Even when the participants have been carefully selected, there are other factors that can lead to clinical studies giving inconsistent results.

- One such factor is the fact that being treated is, in many cases, sufficient to cause an improvement in someone's condition, even if the treatment used does not truly have an effect. This is known as the *placebo effect*, from the Latin *placebo* - 'I will please', since the patient *believes* that they will get better as a result of the treatment, and this may be enough in itself to bring about an improvement.
- Another factor is that people participating in a clinical trial are likely to receive a higher standard of care (more careful diagnosis, more frequent and thorough monitoring, earlier corrective treatment, etc) than those treated outside the context of a clinical trial.

For this reason, most trials, rather than comparing treated with untreated individuals, compare two treatments (A and B) with each other, using two groups of people who are treated at the same time by the same doctors and nurses. The placebo effect would be expected to be the same for both groups, allowing a conclusion to be drawn that treatment A is better or worse than treatment B.

If one of the treatments is known in advance not to be effective (the placebo), the effect of the other treatment can be determined directly. This type of study is called a *placebo-controlled* study. However, if people are ill, and there is an existing treatment available that is known to be effective, it would be unethical to deny them this treatment. It is therefore more usual to compare a new potential medicine against one that is known to work (an *active control*), rather than against a placebo. Indeed, ethical considerations suggest that the active control treatment should be the best one currently available.

Patients and doctors may evaluate their condition more positively, or be more tolerant of side-effects, if they know they are being treated with a new medicine, even though it has not yet been shown to work. ("It's new , so it's got to be better...") To avoid this kind of effect, it is usual for the substances being tested to be made to appear identical, and for their identity to be concealed from both the patients and their doctors until the study is finished and the data has been collected. This type of trial is said to be *double-blind*.

A trial may give a misleading answer if the groups of people being compared are not sufficiently similar to each other. For example, if one group contained people who were older, or had had the study disease for longer, or contained more people of one sex or racial grouping than another, this group might react in a different way to treatment. To avoid this possibility (and the possibility that the person conducting the study might subconsciously sort people felt likely to do better or worse on a given treatment into one group or another), allocation to study groups is conducted in a strictly *random* manner, using a statistical method that can be thought of as being a sophisticated type of coin-tossing. Much trouble is taken to ensure that the various study groups are as similar to one another as possible.

Another important consideration is that all of the procedures and test methods to be used, and all of the items of data that will be collected and analysed to measure a response, should be defined before the trial starts. The key response outcomes to be compared must also be identified in advance. This is done to ensure that data gathering and the treatment given are as uniform as possible throughout the study, and that data are not given special weight just because they look as if they support the hoped-for result. A study of this kind is said to be *prospective* (forward-looking) and is regarded as giving a more reliable result than one in which the methodology was not determined before the start of the study.

Overall, the study type that is regarded as being the most reliable and unbiased is one that is prospective, randomised, controlled and double-blind. Positive results in at least two such trials are normally required, for example, for the FDA in America to grant marketing authorisation to a new medicine.

Study design

A clinical study will normally be designed to answer unique set of questions, and many factors such as cost, practicality, ethical issues and statistical considerations will determine its precise form. How many people should participate and how they should be divided into specific groups is a key consideration. This is a highly specialised aspect of trial design, involving advice from experts in statistics. The total number of study participants needed will depend on the expected size of the treatment effect and how different it is between the groups being compared. If one treatment has a much bigger effect than another, fewer patients will be needed to be sure of finding a real effect than if two treatments have very similar effects.

In the simplest comparative trial, participants are split into two groups and each receives one of two treatments, without knowing which, with the outcomes compared by the investigators at the end of the treatment period. This is called a parallel group study and is a very common design (Figure 6). If the effects of the two treatments are small and similar, large numbers of patients may be required to demonstrate a difference.

If a study participant is already taking an existing medicine, it may be necessary to stop taking it for a period (usually some days), if this can be done safely, before being assigned to one of the treatment groups. This is done to allow the previous medicine's effects to disappear, so that they do not interfere with the actions of those used in the study. Such a non-treatment period is called a wash-out period, as the body is allowed time to eliminate the previous medicine.

A second common study design is one in which a participant receives first one test medicine and then the other in a randomised order. This type of study is called a cross-over study, as participants are crossed over from one medicine to the other (Figure 7). Wash-out periods may also be used in cross-over studies, before treatment is started, or between the first and second treatments.

Cross-over trials might seem to have an advantage over parallel-group trials, as each medicine is tried in each participant, and this might be expected to give more information about their comparative effects. Hence also, a smaller number of participants might be required to detect a given level of difference in effect. However, there are some weaknesses with this approach. For example, it may be that exposure to medicine A affects response to medicine B, but not the other way around, so that the order of treatment becomes significant. Alternatively, in longer trials, the disease itself may have progressed by the time of the second treatment, becoming more or less responsive to treatment, so that the two treatment periods are not equivalent.

Whichever type of trial design is used, participants are free to leave the trial if they feel for any reason that they do not wish to continue. Some people stop participating because of side-effects that occur during the study, while others may find that they are not able to keep to the scheduled hospital/surgery visits, or may move away from the participating study centre before the trial is

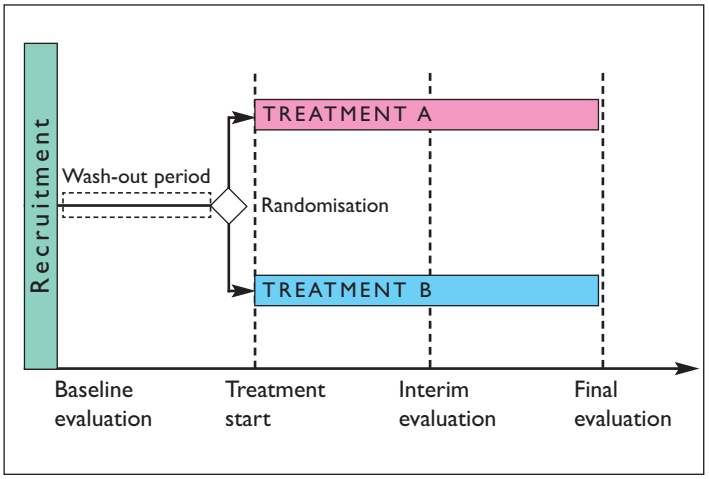


Figure 6: A simple, two-arm parallel group trial design with an initial wash-out period and interim evaluation

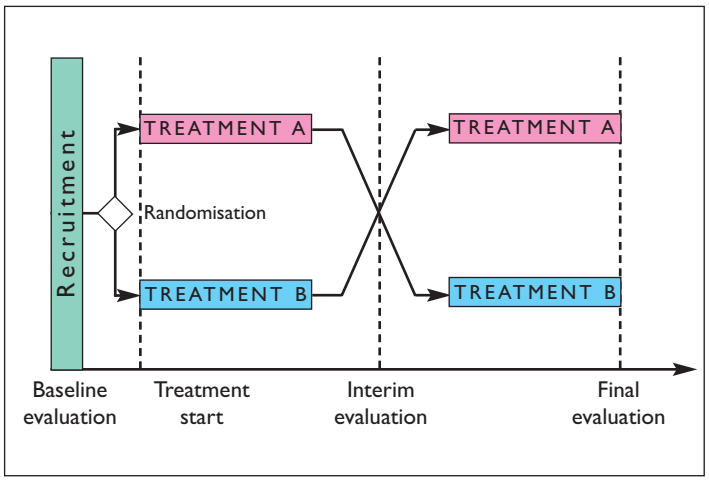


Figure 7: A simple cross-over trial design. A wash-out period could be added, if needed, before randomisation and/or between treatment periods

finished. During a study, they may be given additional medications if the treating doctor feels that this is necessary (for example, if their disease worsens unexpectedly), or, if the trial protocol does not allow this, they may be taken out of the study for further treatment. Studies are run under the principles of the Declaration of Helsinki, which states that participants' wellbeing takes precedence over the gaining of new scientific knowledge.

Who runs clinical trials?

A clinical study can be devised and run by anyone from an individual doctor, through researchers at a medical charity or in universities, or employed by the NHS, to pharmaceutical companies. The UK is seen as a good location for primary care research, since the NHS provides a consistent healthcare structure over a large population base. The great majority of trials of potential new medicines are run by the industry. Industry-sponsored trials are usually performed by investigators in academic medical centres or hospitals who are experts in treating people with the disease concerned, but they may also be carried out by specialised companies (*Contract Research Organisations* or *CROs*) with appropriately qualified staff and experience in the field. EU legislation requires the overall study sponsor to be identified and imposes clear responsibilities on clinical investigators to safeguard the health and safety of trial participants.

Trial approval and monitoring

Before a clinical study can be started, regulatory, ethical and institutional approval must be obtained. For this purpose, an exact description of the planned study (the study protocol) must be written that defines important aspects, such as:

- the objective of the study
- existing evidence about the study questions
- how the study is to be run (trial design and logistics) and by whom
- what measurements are to be made (and when, and how)
- which patients are to be admitted/excluded
- what is already known about the treatments to be used
- how data are to be collected and analysed
- what primary/secondary results (outcomes) will be evaluated
- provisions for privacy, data protection, quality control, study monitoring
- ethical, financial, insurance considerations
- publication policy.

An internationally agreed specification for how clinical studies should be run (Good Clinical Practice, or GCP) and how protocols should be written has been worked out by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). It sets the required standard for studies to be submitted to the regulatory authorities in Europe, the USA and Japan as part of the authorisation procedure for new medicines. It provides an assurance that the rights, safety and wellbeing of trial subjects are protected, and that the study data are credible.

In the UK, approval for the study must be given by the Medicines and Healthcare products Regulatory Agency (MHRA) and by an independent (NHS) research ethics committee, typically made up of doctors, nurses, scientists, members of the public and, sometimes, lawyers. The study must also be approved by the NHS trust for the site, or sites, where it is to be performed. These bodies will check important aspects, such as:

- that the study question is important and cannot be answered from existing evidence
- that the investigators are properly qualified
- that information for patients is adequate and appropriate
- that the study is well designed to answer the study question
- that sufficient resources are available for the trial to be carried out properly and safely
- that the safety and other interests of patients are properly safeguarded
- that it is likely that the benefits of doing the study will outweigh the risks.

As well as these initial approvals, a clinical study is subject to continuous monitoring, to make sure that patient safety is upheld and that the study does not run on beyond the point at which the scientific question has been answered, so that patients are not exposed to treatment unnecessarily. In addition to a trial steering committee, which may include patient representatives as well as the researchers carrying out the study and independent doctors and nurses who supervise the conduct of the trial, there will usually be a completely independent Data Monitoring Committee.

In longer trials, one or more interim evaluations are included in the design, at which point the independent Data Monitoring Committee will decide whether the study should be continued or stopped. If the effect of the treatment under investigation is larger than expected (significantly better than the comparison medication), the committee may decide to stop the study earlier than the investigators had planned. Equally, a trial will be stopped early if one of the medicines produces an unacceptable level of side-effects, or it is clear that the study has no chance of showing a significant difference between the treatments, even if it is continued until the planned study ends.

Finding out about trials

Phase 1 trials usually involve only a relatively small number of participants and these are in most cases people aged less than 45 years without any disease (*healthy volunteers*). Participants in Phase 2 and 3 trials may be older and will have the medical condition under study. They participate on a voluntary basis, after having been given, and confirmed that they have fully understood, information about the trial and the possible risks involved - a process called giving *informed consent* (see below). They are free to withdraw from the trial at any time, without prejudice to their continuing care. Because they will be drawn from the wider community, there must be means of making potential trial participants aware of the existence of new studies. In practice, there are four main routes by which those interested might find out about trials:

1. **Advertising** This is mostly placed at local level in newspapers and on radio stations and through hospital and GP surgery notice boards

2. **Patient groups** and medical charities are often well-informed about new studies that concern their area of disease interest (see, for example: **www.cancerhelp.org.uk/trials/trials/default.asp**)

3. **Direct invitation** through doctors who are already treating people with the relevant condition is a common route for recruiting trial patients

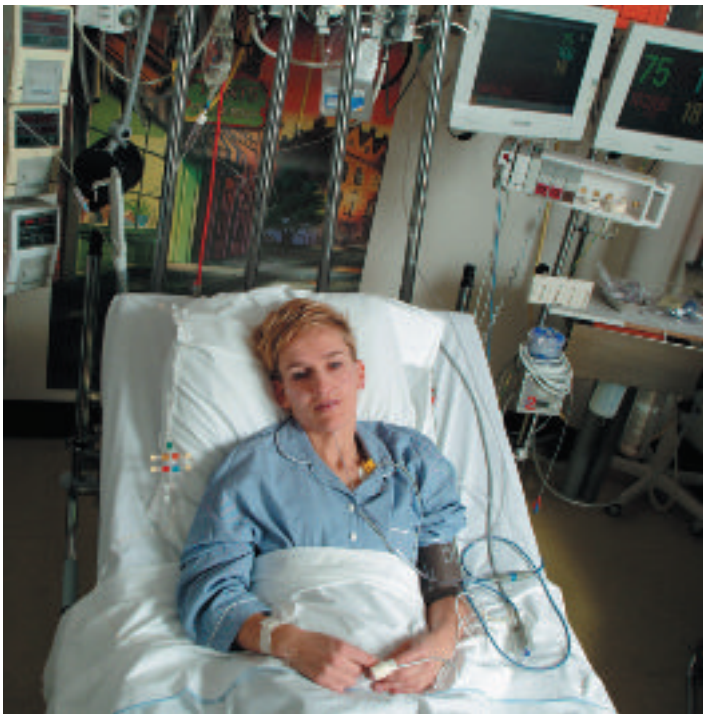
4. **Trial registries** accessible over the internet offer a newer way of finding out about trials.

In 2005 the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), representing the international pharmaceutical industry, launched a portal (**www.ifpma.org/clinicaltrials.html**) for clinical trial registries used by pharmaceutical companies (for example, **www.roche-trials.com/registry.html**) for registering their clinical trials on publicly available websites. This portal also includes information from the clinical trial website run by the National Institutes of Health in the United States (**www.clinicaltrials.gov**) and the ABPI's own trials website (**https://www.cmrinteract.com/clintrial**).

Risks and benefits of trial participation

Participating in a clinical trial of a new medicine entails both possible benefits and potential risks. For example, it has already been noted that a possible benefit of trial participation is that the individual may receive superior medical care during the trial. In addition, treatment with the new compound (if assigned to that treatment group) may produce a better outcome than standard treatment. On the other hand, there may be risks associated with tests used during the study, or with unexpected adverse reactions to the medicines used in the trial. Identifying and explaining these risks and benefits is an important part of the process of obtaining the individual's informed consent to participating in the trial, and the ethics committee that approves the trial will pay especial attention to seeing that such consent is properly obtained.

As part of this procedure, participants will be given a patient information sheet (fact sheet) that sets out the objectives of the trial, what treatments are to be compared, what will be expected of those participating, and possible benefits and risks involved.



Before giving informed consent, there will be an opportunity to ask questions about the trial and the treatments and procedures. It is not the possible to cover such questions here, but typical questions can be found on the website of the charity Cancerbackup (**www.cancerbackup.org.uk/Trials/Understandingtrials/**).

Disease markers and outcomes of clinical significance

With diseases that occur suddenly and progress rapidly, it may be possible to design a clinical trial so that it covers much of the clinically relevant time period. It will then be clear, by the end of the trial, whether a treatment has made a participant better or not. When a disease progresses slowly, however, it may be many years before the outcome is clear. It would be very costly and difficult to run a trial long enough for there to be a significant number of events to use to differentiate one treatment from another.

One example of this is the treatment of high blood pressure. High blood pressure arises in response to other gradual disease processes, such as progressive narrowing of the arteries, and is a convenient marker of the underlying disease. High blood pressure itself does not necessarily cause any observable clinical symptoms, but it is already known from long studies such as the Framingham study that people with high blood pressure are more likely to have a heart attack, stroke, or cardiovascular-related death. Moreover, it is also known that lowering blood pressure with a medicine will reduce the chance of such events happening. In testing a new type of medicine for high blood pressure, it would therefore be sufficient to measure its effect on blood pressure, which is usually apparent within a few days or weeks, rather than running a study of, perhaps, 10-20 years duration, to measure its effect on the ultimate clinical outcomes such as stroke or death.

There are many other markers that are measured in trials to show an effect of treatment. While high blood pressure is a well-established risk factor for cardiovascular events, some of these

other markers may not be so well established, and regulatory authorities may demand longer studies that do use clinically significant events as outcomes for judging whether a new medicine is effective enough to be given approval. Indeed, even with medicines for high blood pressure, such large long-term trials have increasingly been required. This has, in turn, considerably increased the cost and time taken before the medicines can be made available for use.

Why medicines may fail in development

At each stage in the clinical development of new medicines, some compounds are discontinued. Phase 1 trials focus on how well a compound is tolerated and, as might be expected, almost half of the compounds dropped at this stage are discontinued because they were not tolerated well enough to be clinically useful. Phase 2 trials are mainly concerned with finding the best dose and looking for signs that it is effective as a treatment. Unacceptable side effects are a less common reason for stopping development at this stage; instead, the leading reason for discontinuation is that the medicine was not effective enough. Poor absorption, metabolism or unsuitable dosage form are also a significant reason for stopping development. Nevertheless, compounds that enter Phase 2 trials have a good chance (ca. 1 in 4 or 5) of eventually being approved.

In Phase 3 trials, the main focus is on establishing efficacy and safety as compared with existing treatments. Insufficient efficacy or an unfavourable safety profile remain the leading reasons for stopping development. Tolerability is still an issue at this stage because, as development progresses, a wider spectrum of patients is exposed to the compound, and this may show up effects not seen in smaller trials, or when the compound is given for a shorter period. The great majority of compounds that complete Phase 3 trials successfully are subsequently authorised for clinical use.

Trial results

When a trial has been completed, the investigators who organised it will want to publish the results in some way. The study organisers may also provide information to participants about the final results, although this is not automatic.

Under proposals drawn up by the world's major pharmaceutical industry trade associations and agreed by major companies, results of all industry-sponsored clinical trials on medicines that have received marketing authorisation, and which evaluate its safety and benefit, will be publicly disclosed via free, widely accessible databases, regardless of outcome. Also, details of all clinical trials being performed to determine a medicine's therapeutic benefit will be publicly registered at initiation so that patients and clinicians will have information about how to enrol. Both requirements were adopted by the worldwide pharmaceutical industry during 2005.

The results are published in a standard, non-promotional summary that includes a description of trial design and methodology, results of primary and secondary outcome measures described in the protocol, and safety results. However, if the results are also published in a peer-reviewed medical journal, the database will alternatively include a link to the relevant article and, in some cases, the summary as well. By publishing not just the results of trials that have taken place and also those that are just starting, a major step has been taken towards achieving greater transparency. The results should normally be published within one year after the medicine is authorised or, for post-authorisation trials, within one year of them being completed. Information is on the clinical trials website of the international industry association (**www.ifpma.org/clinicaltrials.html**).

When an application for marketing approval is made, a company must provide all trials results, whether positive or negative, to the licensing authorities. A summary of this information is made available to the public on the granting of marketing authorisation. This summary, called a European Public Assessment Report (EPAR) is produced by the European Medicines Evaluation Agency (EMEA), and is accessible through the EMEA's website (**www.emea.eu.int/htms/human/epar/epar.htm**). For medicines authorised by the MHRA in the UK, the Public Assessment Report (UKPAR) is available on the MHRA website (**www.mhra.gov.uk**).

Now read on.....

This booklet attempts to give a snapshot of where medicines research stands on a global basis in major disease areas, and of what may lie in store over the next few years. Inevitably, this tends to focus on the new active substances that are in companies' research pipelines, but it should not be forgotten that no progress could be made in this important endeavour without the active collaboration both of researchers and clinicians in institutes and hospitals outside the industry and, especially, the commitment of all those who take part as subjects in the many trials mentioned here. It is thanks to them, as much as to industry, that progress continues to be made in overcoming the burden of disease.

The *A to Z of Medicines Research* shows that the pharmaceutical industry is strong in terms of creativity and diversity. There remain many diseases for which doctors lack cures and treatments, but there has been great progress over the past twenty years in improving treatments for major killers such as heart disease, diabetes and leukaemias. Even where cures are not yet in sight, however, access to better medicines has transformed the prospects and quality of life of many patients with breast cancer, HIV infection, osteoporosis, psoriasis, viral hepatitis and other conditions, and the expertise of British researchers and clinicians has made a significant contribution towards such progress. Responding to these challenges with a keen eye on the future, British medicines development has the potential to build further on its reputation as a world leader over the next 50 years.

A-Z of medicines research

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A

ALZHEIMER'S DISEASE

What is Alzheimer's?

Alzheimer's disease is the commonest cause of **dementia** - a group of progressive conditions which involve memory loss (especially short-term memory), poor concentration, poor sense of time and space, difficulty in finding words or understanding other people, difficulty in perceiving and interpreting surroundings, mood changes and emotional upsets. As their condition worsens, people with dementia may get lost, engage in inappropriate behaviour or become unable to carry out simple everyday tasks. Eventually, they may show personality loss and become dependent on others. Alzheimer's disease accounts for 62 per cent of all cases of dementia. Vascular dementia, caused by damage in the brain following blockages in blood flow, accounts for a further 20 per cent.

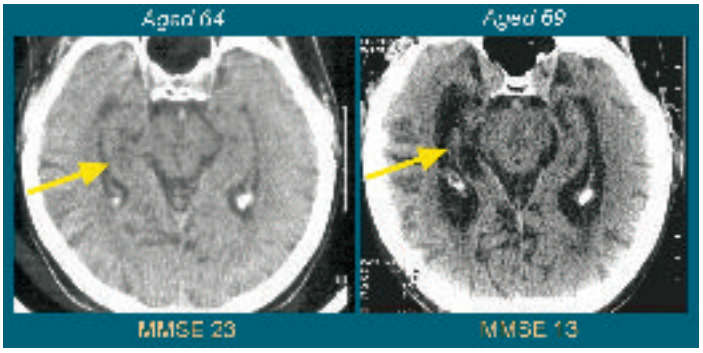

Figure 1: **Computed Tomography (CT) scan of a patient with confirmed Alzheimer's disease. Shrinkage of the hippocampus (arrowed) strikingly parallels cognitive decline as assessed by the Mini-Mental State Exam (MMSE) score.**
(Picture courtesy of Professor AD Smith, OPTIMA, Oxford University)

Figure 2: **Researcher examining a microscope section stained to reveal neurofibrillary tangles and senile plaques in the brain of a patient with Alzheimer's disease**

It is difficult to diagnose Alzheimer's with certainty. Diagnosis is based on excluding other causes of dementia and on medical history. Computed Tomography or Magnetic Resonance Imaging scans of the brain show tissue loss over time, especially in the hippocampus (Figure 1), and, in advanced cases, brain shrinkage. However, these methods are not sufficient for a conclusive diagnosis. This is only possible after death, when microscopic examination of brain sections shows characteristic protein deposits inside brain cells (neurofibrillary tangles) and outside them (senile plaques).

Who does Alzheimer's affect and what does it cost?

Dementia affects as many as 5 per cent of people over 65, rising to 20 per cent over the age of 80. More than 400,000 people in the United Kingdom are estimated to suffer from Alzheimer's, some 80,000 of them with mild disease and the remaining 320,000 with moderate to severe disease. Aging of the population is expected to lead to a steady increase in the number of people affected by Alzheimer's, placing an increasing burden on their families and all parts of the healthcare system. Alzheimer's is, however, not simply a natural consequence of aging but a physical disease. A great deal has been learned in the past decade about factors that raise or lower the risk of the disease and about the biochemical basis of Alzheimer's, and this has resulted in a big increase in efforts to find better treatments.

The costs of caring for people with Alzheimer's disease are difficult to estimate. Costs also depend markedly on the stage of disease. The NHS bears relatively little of the cost of dementia, with local authorities and individuals (patients and their relatives) funding much of the care. Caregiving time and lost earnings for family carers make up the largest part of the costs, followed by the cost of professional carers. The total cost of providing care for Alzheimer's has been estimated at more than £6 billion per year, while expenditure on medicines for this condition in 2004/05 was approximately £60 million (about £1,000 per patient per year).

Present treatments and shortcomings

There is currently no cure for Alzheimer's. However, it has been known for some time that levels of a chemical messenger (a *neurotransmitter*) called acetylcholine (ACh) that acts in the brain (site 1, Figure 3) are reduced by 20-40 per cent in people with Alzheimer's, and medicines that prevent breakdown of ACh by inhibiting the enzyme acetylcholinesterase (AChE) can help with treatment of symptoms in those whose disease is not too far advanced.

Three AChE inhibitors are currently available in the United Kingdom: donepezil (Aricept, Eisai and Pfizer), rivastigmine (Exelon, Novartis) and galantamine (Reminyl, Shire). Clinical trials have shown that about 10-30 per cent of patients show an improvement with these medications compared with placebo treatment in one or more areas of measurement such as cognition, global functioning and daily activities. Gastrointestinal side effects (nausea, vomiting, diarrhoea) are the most common adverse reactions.

Memantine (Ebixa, Lundbeck), developed by Merz Pharma, is the fourth medicine to be made available for use in Alzheimer's. It is

NEW SINCE 2000

2001 - Rivastigmine oral solution (Exelon, Novartis)

2002 - Memantine (Ebixa, Lundbeck)

an inhibitor of the NMDA receptor in the brain, which responds to glutamate, another chemical messenger that is involved in memory and learning (site 6, Figure 3). Memantine has been shown to produce cognitive and behavioural improvement in the more advanced stages of Alzheimer's where AChE inhibitors may be less effective.

The use of these medicines has recently been called into question by a ruling from the Government's National Institute for Health and Clinical Excellence (NICE) that they do not meet criteria for cost-effectiveness and should be prescribed on the NHS only on a restricted basis (AChE inhibitors) or not at all (memantine). This conclusion has been strongly criticised by organisations representing doctors and patients, as it does not take into account the benefits of these medicines to patients and their carers/families that are not reflected in costs accruing to the NHS.

What's in the development pipeline?

Further research continues on AChE inhibitors. Novartis has a rivastigmine skin patch in Phase 3 development, which may be more suitable for use in people with Alzheimer's than tablets, which patients may forget to take. Eisai has conducted Phase 3 trials that showed that donepezil is also effective in those with severe Alzheimer's disease.

Huperzine-A is an agent developed from Chinese herbal sources that also inhibits AChE. Neuro-Hitech Pharmaceuticals is testing it in Phase 2 trials in the United States. The company is also developing a skin patch form, while DebioPharm has a form (ZT-1) of Huperzine-A in Phase 2 trials which is taken by mouth. This compound has also been claimed to have nerve-sparing properties as well as inhibiting AChE.

Also in the US, Torrey Pines Therapeutics is exploring Posiphen in Phase 1 trial. This compound has a dual action in Alzheimer's. In addition to being a selective AChE inhibitor, it has been shown to inhibit the formation of beta-amyloid precursor protein (site 4, Figure 3), which is the starting point for the formation of the characteristic amyloid plaques seen in the brain of patients with Alzheimer's. The company also has a compound (bisnorcymserine) in preclinical development that inhibits another ACh-metabolising enzyme.

AChE inhibitors help to prolong independent living and reduce the burden on carers, but they do not provide a long-term solution to the treatment of Alzheimer's. The eventual goal must be to develop medicines that modify the course of the disease.

Compounds which may do this can be grouped according to the sites at which they act (Figure 3). Medicines acting at site 2 mimic nerve growth factor (NGF) and are taken up at nerve

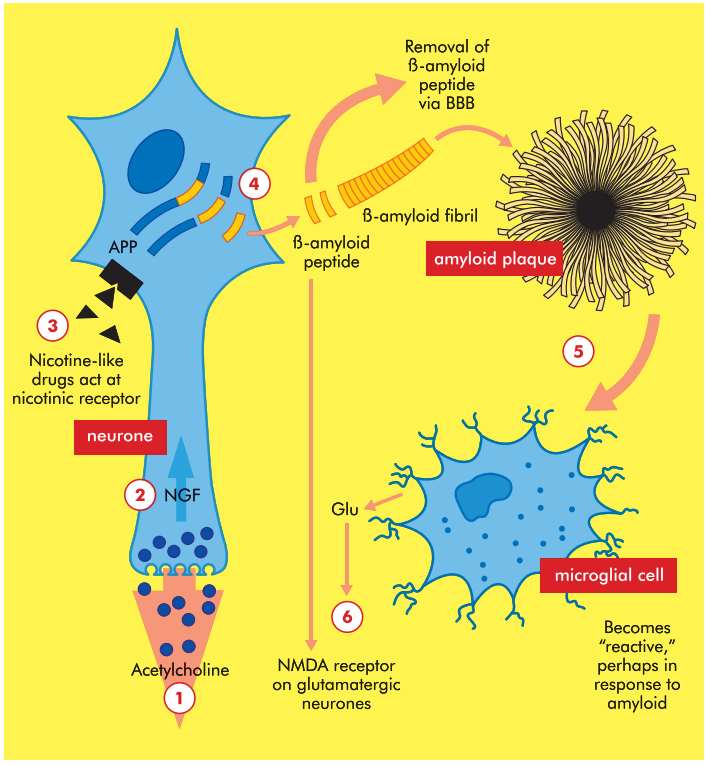

Figure 3: **Some sites at which Alzheimer's medicines may act.**

endings, where they promote repair. Those acting at site 3 stimulate neuronal nicotinic (N) receptors and may also protect nerve cells. Those that act at site 4 prevent plaque formation by modulating its production or clearance, while others may act at site 5 to damp down the secretion of neurotoxic (nerve damaging) compounds by glial cells. One of these neurotoxic compounds is glutamate. This is an important neurotransmitter in the brain that acts via specific (NMDA and other) receptors (site 6) on certain neurones. However, high concentrations of glutamate are toxic and this toxicity is amplified by beta-amyloid protein. Beta-amyloid protein is normally removed from the brain by being transported through the blood-brain barrier, but this barrier is damaged in Alzheimer's disease and excess beta-amyloid protein accumulates in characteristic senile plaques in the brain.

Of the medicines in development that act in a nerve growth factor-like manner, or which stimulate production of NGF (site 2, Figure 3), the most advanced are Ebewe's cerebrolysin, which is in Phase 3 trial, and the oral agent SR 57746 (Xaliproden) from sanofi-aventis, also in Phase 3, which stimulates the production of naturally occurring NGFs. In addition, sanofi-aventis is researching another once-a-day oral compound of the same type (SR 57667, paliroden) which is now in Phase 2 trials. Another small molecule candidate with NGF-like properties is T-817MA from Toyama Chemical, now at Phase 1.

Compounds that activate some of the nicotinic ACh receptors in the brain (site 3, Figure 3) have been shown to improve cognition and memory. Such medicines are being developed by several companies. Abbott has ABT-089 in Phase 2 trial in patients with Alzheimer's and Targacept, in collaboration with AstraZeneca, has the compound TC-1734 (AZD 3480) at the same stage. Athenagen's GTS-21 is in Phase 1 trial and Memory Pharma has MEM 3454 at the same stage, while sanofi-aventis has SSR 180711 in Phase 1 development.

Much research has been directed towards developing medicines that can affect the formation and breakdown of amyloid protein plaques (site 4, Figure 3). Generation of beta-amyloid peptide from amyloid precursor protein is an early step in this process and agents that inhibit the enzyme gamma secretase would be expected to block this process and reduce plaque formation. Eli Lilly's gamma secretase inhibitor LY450139 is entering Phase 3 study, while Eisai is just starting Phase 1 trials with its agent E-2012.

Several other approaches are being taken to inhibiting amyloid plaque formation. Tramiprosate (Alzhemed, Neurochem) is a small molecule that binds to beta-amyloid peptide and prevents its deposition in plaque, as well as reducing its potential to damage nerve cells. A Phase 3 study with this agent has been started in patients with mild-to-moderate Alzheimer's. TransTech Pharma also has a candidate medicine that reduces beta-amyloid levels, and this has reached Phase 2 trial.

Other attempts to block or reverse plaque formation involve passive or active immunisation. Elan and Wyeth are studying an anti-amyloid beta monoclonal antibody (AAB-001, bapineuzumab) in Phase 2 trials. Other companies have similar antibodies at the Phase 2 (Eli Lilly) or Phase 1 stage (Roche), while Novartis and Cytos Biotechnology are collaborating on the Phase 1 development of a vaccine (CAD106) that will generate anti-amyloid antibodies. Elan and Wyeth also have an active immunity candidate (ACC-001) at Phase 1. Animal studies have shown that specific antibodies against beta-amyloid can dissolve pre-existing plaques and it is hoped that such an immunological approach may offer a real prospect of halting or even reversing the course of disease.

Non-steroidal anti-inflammatory drugs (NSAIDs) have shown signs of being able to reduce inflammation in brain cells in Alzheimer's (site 5, Figure 3) but some of this class of medications (Cox-2 inhibitors) have been found to have side-effects that make them unsuitable for long-term, high-dose use. R-flurbiprofen (Flurizan, Myriad Genetics) is an NSAID of low anti-inflammatory activity but with an ability to reduce levels of beta-amyloid through inhibition of gamma secretase. It has reached Phase 3 trial in early-stage Alzheimer's.

Another compound similar to memantine which also has inhibitory activity at NMDA-type receptors for the neurotransmitter glutamate (site 6, Figure 3) has reached clinical trials in Alzheimer's. Merz Pharma and Forest Labs have neramexane in Phase 3 trial.

Serotonin (5-HT) is another neurotransmitter that is thought to play a role in cognition and GlaxoSmithKline has 742457, an antagonist that is highly specific for $5HT_6$ receptors, in Phase 2 study. Wyeth's lecozotan, a $5HT_{1A}$ receptor antagonist, is also at Phase 2, as is the $5HT_4$ agonist (PRX-03140) from EPIX Pharma. It has been suggested that medicines affecting 5HT receptors may be helpful in addressing some of the behavioural and psychological symptoms of Alzheimer's, but development of these compounds is not yet far enough advanced for their value to have become clear.

Other neurotransmitter pathways are also being explored for their therapeutic potential. Muscarinic (M_1) receptors have also been implicated in memory and learning, and Torrey Pines Therapeutics has a selective M_1-agonist (NGX267) in Phase 1 development. An increased level of the dopamine- and noradrenaline-degrading enzyme monoamine oxidase-B (MAO-B) has been found in Alzheimer's, and several compounds that inhibit it are being investigated. Teva's ladostigil tartrate is a selective MAO-B inhibitor that also helps to protect nerves and inhibit AChE. It has reached Phase 2 trial, as has the company's other MAO-B inhibitor rasagiline, which is already available for use in Parkinson's disease. Of the other transmitters, UCB is exploring a GABA analogue (Piracetam) in Phase 3 trial for mild cognitive impairment, Saegis Pharma has a $GABA_B$ receptor antagonist (SGS742) at Phase 2 for mild-to-moderate Alzheimer's, and sanofi-aventis is exploring the selective CB1 antagonist AVE1625, which has reached Phase 2 trial.

Lastly, there are some existing medications, indicated for other uses, that have shown preliminary evidence of being able to decrease the risk of developing Alzheimer's, and formal clinical trials are now in progress to evaluate their ability to affect the course of established disease. Several studies had indicated that the cholesterol-lowering statins may have such an activity, and Pfizer is conducting a Phase 3 study of atorvastatin (Lipitor), in mild-to-moderate Alzheimer's. Similarly, insulin resistance (seen in type 2 diabetes) has been found to correlate with the risk of developing Alzheimer's and glucose metabolism is known to be abnormal in those with the disease. A small study had shown that the insulin-sensitiser rosiglitazone XR (GlaxoSmithKline) produced a significant cognitive improvement in Alzheimer's patients lacking the apo-lipoprotein E-4 gene. GSK has started a Phase 3 study of rosiglitazone in mild-to-moderate Alzheimer's.

The longer-term future

Interest in developing new treatments for Alzheimer's remains intense, fuelled by recent discoveries about the disease processes, and a great number of alternative approaches are under investigation in earlier-stage clinical and preclinical trials by companies such as Pfizer (PF-4494700, Phase 2), Dainippon-Sumitomo (AC-3933, Phase 2), Memory Pharma (MEM1003, Phase 2), Accera Inc (AC-1202, Phase 2), Prana Biotech (PBT-2, Phase 1), AstraZeneca (AZD 1080, Phase 1) and others. With this degree of investment of research effort, future prospects for a treatment that can slow or halt the progress of Alzheimer's would seem encouraging.

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ANXIETY

What is anxiety?

Anxiety is a normal response to a dangerous situation, and helps ensure we avoid physical and mental damage. However, severe and/or persistent anxiety in situations where it is not appropriate can impair everyday life and social relationships and becomes an anxiety disorder. Symptoms of anxiety disorders include nervousness, sweating, trembling, palpitations, fear/panic, irritability and sleep disturbances.

There are several different types of anxiety disorder, including:

- Generalised anxiety disorder (GAD)
- Panic disorder
- Social phobia
- Obsessive-compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD).

Some anxiety disorders have specific triggers, appearing in response to specific situations (e.g. fear of public speaking), but others, such as panic attacks and GAD, do not seem to be related to an overtly threatening situation. Generalised anxiety disorder is the most common form of anxiety. Anxiety also often accompanies depression (see *Depression*). Panic disorders more commonly lead to people seeking medical help, however, because of the suddenness and severity of the symptoms.

Who does anxiety affect?

Generalised anxiety disorder and panic disorder most commonly occur for the first time when people are in their late teens or twenties. Social phobias and OCD, by contrast, often start during childhood or adolescence. Anxiety (including mixed anxiety and depression) affects women more often than men, whereas the other disorders affect men and women about equally. A survey in 2000 found that approximately 4.4 per cent of adults (aged 16-74) were affected by GAD, with a further 8.8 per cent experiencing mixed anxiety and depression.

NEW SINCE 2000

2005 - Escitalopram (Cipralex, Lundbeck)

2006 - Pregabalin (Lyrica, Pfizer)

Present treatments and shortcomings

Treatments for anxiety may be broadly divided into psychological therapies and medicines, complemented by self-help and relaxation techniques. Cognitive behavioural therapy (CBT), where available, is the recommended psychological therapy for both generalised anxiety disorder and panic disorder. Where immediate treatment is needed for rapid control of symptoms, short-term use of a benzodiazepine or a sedating antihistamine is recommended for GAD, and an SSRI antidepressant is recommended for panic disorder (benzodiazepines are not recommended in this case). For longer-term treatment, an SSRI antidepressant is recommended in both GAD, and panic disorder. Paroxetine (Seroxat, GSK) and escitalopram (Cipralex, Lundbeck) are specifically available for these conditions; a greater range of antidepressants, including tricyclics, are available for use in mixed anxiety and depression. Pregabalin (Lyrica, Pfizer) is also available for generalised anxiety disorder.

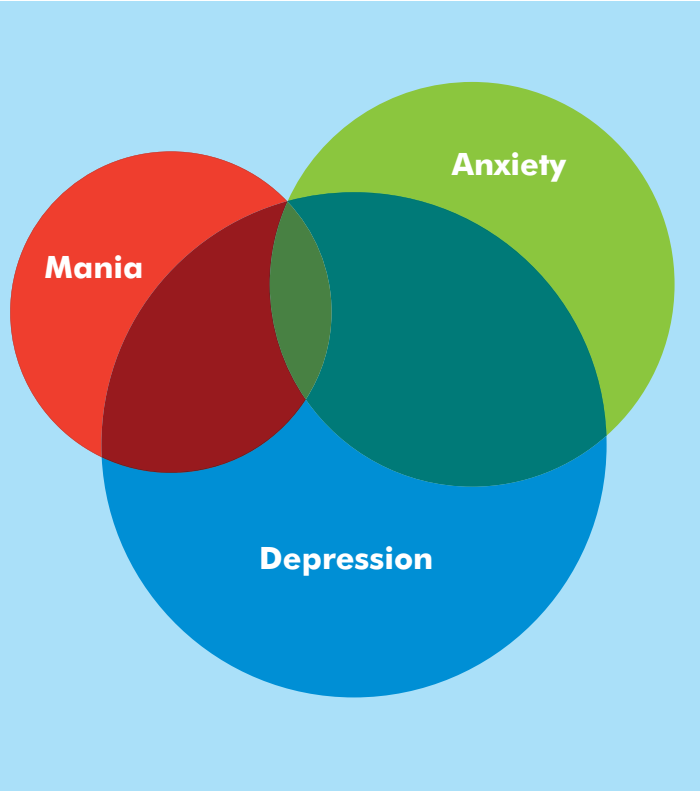

Figure 1: **Anxiety occurs alone (GAD), together with depression (mixed), during depressive episodes of bipolar disorder, or between manic and depressive episodes.**

What's in the development pipeline?

Although the way they work is not entirely understood, a number of antidepressant medicines have been found to be helpful in reducing anxiety. So a number of compounds intended for treating depression are also being tested in anxiety disorders. Typically, these are medicines that interact with neurotransmitters in the brain, such as serotonin (5HT) and noradrenaline (NA), that are believed to be involved in mood and emotion. For example, the dual 5HT/NA reuptake inhibitor duloxetine (Cymbalta, Lilly) that has been indicated for use in depression is currently in Phase 3 trial for GAD. Another $5HT_{1A}$ agonist (MN-305, MediciNova) is in Phase 2 trials. Also in Phase 3 trial for GAD are quetiapine (Seroquel SR, AstraZeneca), which is a dual dopamine-D_2 and

$5HT_2$ receptor antagonist, and agomelatine (Servier and Novartis) a $5HT_{2C}$ antagonist and $MT_{1/2}$ (melatonin) receptor agonist, which is also in Phase 3 trials for depression.

Neurokines (NK) are other neurotransmitters that may be involved in anxiety and several experimental compounds that target them are being tested in anxiety disorders. An antagonist is a substance that blocks a chemical process in the body, such as the binding of a neurokine to its receptor. **NK_1 receptor antagonists** under study in Phase 2 trials include LY686017 (Lilly) in social phobia, and GSK679769 (casopitant, GSK) in anxiety. In addition, GSK has another compound (GW823296) in Phase 1 study. Sanofi-aventis also has an **NK_2 receptor antagonist** (Saredutant) in development for treating anxiety and this has reached Phase 3 trial.

Another class of compounds that is being intensively studied in anxiety states is that of selective inhibitors of receptors for a substance called corticotropin releasing factor (CRF), which is involved in response to long-term stress. **CRF_1 receptor inhibitors** are at an earlier stage in development than NK_1 receptor antagonists, with the most advanced being GSK876008 (Phase 2) and GSK 561679, under development by GSK, Ono Pharma's ONO 2333Ms, SSR 125543 from sanofi-aventis and TS-041 from Taisho and Janssen, in Phase 1 trials. In addition, Bristol-Myers Squibb has DMP696 and DMP904, that have shown promise in preclinical models.

Glutamate is a major neurotransmitter in the brain and limbic structures in the brain that are involved in the control of emotions and carry a type of receptor known as **metabotropic glutamate** receptors. Several companies are exploring antagonists of such receptors and Lilly's LY544344 has already reached Phase 3 trial. The company has another compound of this type (LY354740) in Phase 2 study. Other companies are investigating compounds at Phase 1 that bind to the type 5 subclass of receptors, including Addex Pharma (ADX-10059) AstraZeneca (AZD 2066) and Novartis (AFQ 056).

A considerable variety of other approaches are also being explored and tested, including:

- Adrenergic beta-3 receptor agonist (SR 58611, sanofi-aventis; Phase 2)
- Benzodiazepine agonist (XBD 173, Novartis; Phase 2)
- Alpha-2 delta calcium channel blocker (PD-332334, Pfizer; Phase 2)
- Vasopressin-1B antagonist (SSR 149415, sanofi-aventis; Phase 2)
- Phosphodiesterase-2 inhibitor (ND7001, Neuro3d; Phase 1)
- G-protein-coupled receptor modulator (R7090, Roche; Phase 1)
- GABA-A antagonist (TP003, Merck Sharp & Dohme; Phase 1)
- Mixed $5HT_1$ antagonist (163090 and 588045, GSK; Phase 1)
- Enkephalin receptor modulator (AZD 2327, AstraZeneca; Phase 1)
- Fatty acid hydrolase inhibitor (SSR 411298, sanofi-aventis; Phase 1)
- $5HT_6$ receptor agonist (WAY-181187, Wyeth; Phase 1).

There is a rich pipeline of new compounds being explored for the treatment of anxiety and the coming years promise to bring a worthwhile expansion of the options available. Nevertheless, in anxiety as well as in depression, psychological therapies and supportive and self-help measures will continue to play an important role in treatment.

FOR FURTHER INFORMATION CONTACT:

Anxiety Care,
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OR

Triumph over Phobia (TOP UK),
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Website: www.triumphoverphobia.com

ASTHMA

What is asthma?

Asthma is a group of disorders involving inflammation and constriction of the airways in the lungs, leading to the production of thick mucus which impairs breathing. Asthma attacks may be triggered by many substances to which people are allergic (allergens), or by anxiety, cold air, exercise and chemicals such as sulphur dioxide. Asthma provoked by allergens is known as 'extrinsic' asthma, and involves a blood protein called immunoglobulin E (IgE). Extrinsic asthma is estimated to account for 80 per cent of cases of asthma in children and more than half of those in adults. People with asthma but no apparent allergy are said to have 'intrinsic' asthma. Acute asthma with severe constriction of the airways is a dangerous condition, often needing hospitalisation and emergency treatment.

Who does asthma affect and what does it cost?

Asthma incidence in the United Kingdom has increased markedly in recent years and an Asthma UK audit has found that 1 in 10 children and 1 in 12 adults are currently being treated for asthma, a total of 5.2 million people, of whom half have severe symptoms. In severe cases, the symptoms of asthma are intense and frequent enough to cause significant restrictions on many aspects of daily life. Asthma causes over 78,000 hospital admissions and about 1,400 deaths each year. It is the most frequent cause of being off sick from school and among the most common reasons for GP visits. The total cost to the NHS of treating asthma averages £889 million per year. In addition, over 20 million working days are lost due to asthma each year, costing the economy some £2.5 billion.

Present treatments and shortcomings

Present medications can be divided into two main categories - bronchodilators and anti-inflammatory compounds, mostly given by inhalation. The bronchodilators may be grouped broadly into:

- **short-acting beta$_2$ stimulants (agonists):** salbutamol (Ventolin, Allen & Hanburys) and terbutaline (Bricanyl, AstraZeneca), mainly used for symptom relief as required
- **long-acting beta$_2$ agonists (LABA):** salmeterol (Serevent, Allen & Hanburys), formoterol (Foradil, Novartis and Oxis, AstraZeneca) and bambuterol (Bambec, AstraZeneca)
- **anticholinergics:** short-acting ipratropium (Atrovent, Boehringer Ingelheim) and long-acting tiotropium (Spiriva, Boehringer Ingelheim)

while the anti-inflammatory compounds are comprised of:

- **corticosteroids:** beclometasone (e.g. Becotide, Allen & Hanburys), budesonide (e.g. Pulmicort, AstraZeneca), fluticasone (Flixotide, Allen & Hanburys), ciclesonide (Alvesco, Altana) and mometasone (Asmanex, Schering-Plough)

and some other agents, including montelukast (Singulair, Merck Sharp & Dohme) and zafirlukast (Accolate, AstraZeneca). There are also a number of inhaled products containing both a bronchodilator and an anti-inflammatory agent. Also, a monoclonal anti-IgE antibody (Xolair, Novartis) is available for use with steroids in severe and persistent allergic asthma.

NEW SINCE 2000

2000 - Salmeterol + fluticasone MDI (Seretide Evohaler, Allen & Hanburys)

2001 - Budesonide + formoterol (Symbicort Turbohaler, AstraZeneca)

2003 - Mometasone (Asmanex, Schering-Plough) for persistent asthma

2003 - Montelukast granules (Singulair Paediatric Granules, MSD)

2005 - Ciclesonide (Alvesco, Altana)

2005 - Omalizumab (Xolair, Novartis)

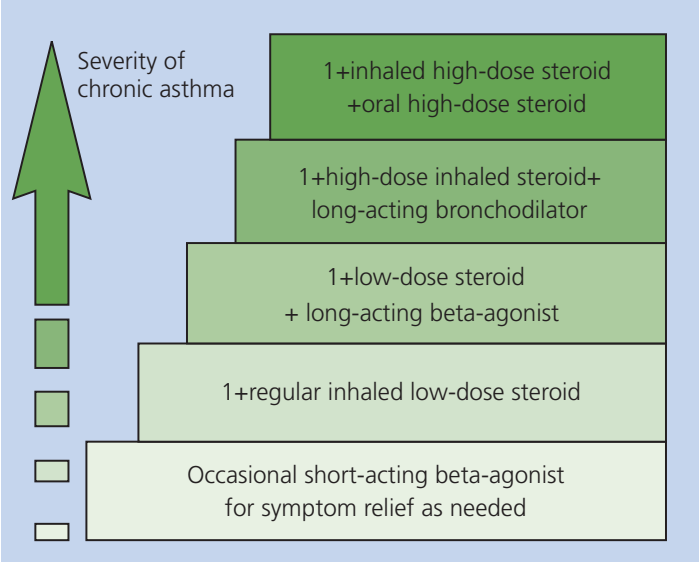

Figure 1: **Summary treatment guidelines, according to the severity of chronic asthma.**

Guidelines for the use of these medicines in chronic asthma advocate a cascade approach, starting with the minimal dose of a beta$_2$-agonist (bronchodilator) needed to control symptoms, progressing to low-dose steroids (anti-inflammatory), higher dose/frequency steroids, then the addition of other bronchodilators to reduce the steroid requirement and, finally, adding oral steroids. The shortcomings of these agents are dependent on their type. Recent clinical studies have suggested that existing long-acting beta agonists, for example, may increase the risk of developing severe asthma and caution is therefore required in their use. Another significant problem in treatment is limited response, or the development of tolerance, requiring gradually stronger medication.

What's in the development pipeline?

An allergic reaction in extrinsic asthma (Figure 2) involves two stages: sensitisation and activation. Sensitisation occurs when allergens (e.g. pollen grains, animal hairs, scales or faeces of the house dust mite, types of food, etc.) are processed in the body by specialised cells which then overproduce IgE antibodies specific for each allergen. IgE circulates in the blood and eventually attaches to mast cells and eosinophils in the lungs. This stage does not cause any symptoms, but will have primed the individual concerned for the future.

An asthma attack follows activation (Figure 2), which occurs when the patient is exposed to the allergen again, when it binds to the specific IgE on the mast cells and eosinophils. These then respond by releasing molecules (leukotrienes, platelet activating factor, complement components, cytokines and neuropeptides) that cause the airway constriction and inflammation that signal an asthma attack. With successive attacks, the accumulation of these and other potentially inflammatory cells gets worse and a deteriorating spiral starts. Ultimately, this may lead to chronic asthma that is less responsive to treatment.

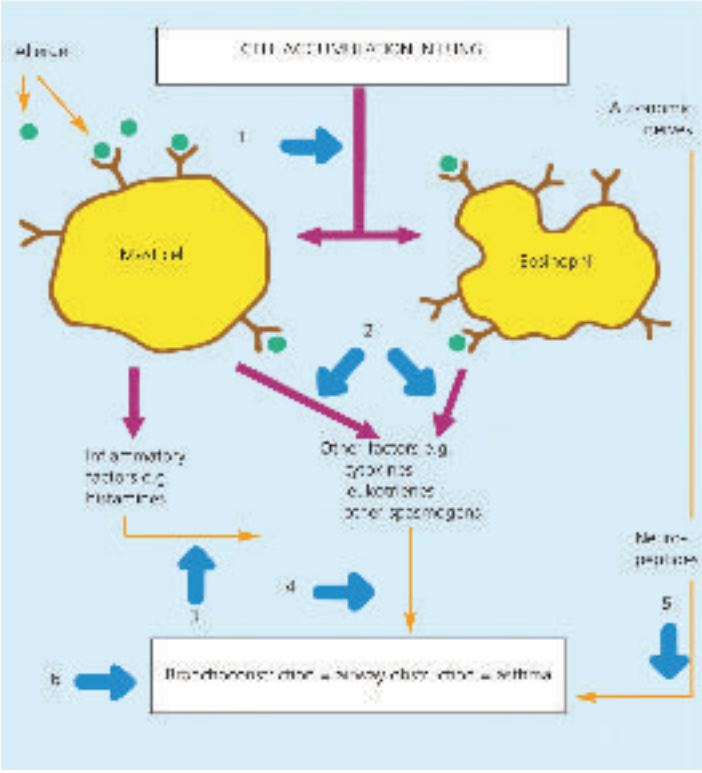

Figure 2: **Some of the cells and chemical messengers involved in an asthma attack. The numbers are the sites at which asthma medicines act.**

Allergic rhinitis (hay fever) has similar causes to asthma, but the allergic process occurs in the upper respiratory tract instead of the lung and does not lead to similarly severe consequences.

With such a complex process, there are many possibilities for new therapies (Figure 2, arrows 1 to 6). A significant amount of research is aimed at developing improved ways of delivering existing medicines into the lung, since inadequate dosing of prescribed medicines is a problem for the patient and a major cause of unsatisfactory treatment. GlaxoSmithKline's dry power inhaler combining fluticasone and salmeterol (Seretide Diskus) and AstraZeneca's combination of budesonide and formoterol (Symbicort pMDI), are examples of such developments.

Other research aims to develop new chemical substances for asthma therapy. Some of the possible approaches are outlined below.

1. Prevention of cell accumulation in the lung (Fig 2, arrow 1):
Cells are attracted to inflammatory sites through chemical signals. Blocking the formation of the signal substances or slowing cell responsiveness to them can reduce cell accumulation. This is one of the ways in which phosphodiesterase (PDE) inhibitors act. Several companies have them in development. Nycomed is conducting Phase 3 trials of the oral **PDE-4 inhibitor** roflumilast, while Glenmark has another agent of this type (oglemilast) in Phase 2 studies. Ono Pharmaceuticals also has an oral PDE-4 inhibitor (ONO-6126) in Phase 2 study and GlaxoSmithKline is investigating an inhaled compound (GSK 256066) at Phase 2 for both asthma and allergic rhinitis. Tolerability problems have hampered development of earlier oral PDE-4 inhibitors, and administration by the inhaled route may therefore have some advantages.

Cell recruitment is a multi-step process, and several other compounds in development are designed to interrupt these pathways. Selectins are receptors on cells that are involved in the adhesion of inflammatory cells in the early steps of their migration into the lung. Revotar's pan-selectin inhibitor bimosiamose is being studied for its ability to prevent this process, and has now reached Phase 2 trials. Inflazyme Pharma's oral IPL512,602 is also in Phase 2 study.

2. Agents blocking the production or release of inflammatory molecules (Fig. 2, arrow 2):
Many small inflammatory molecules are released in chronic asthma. These include leukotrienes (LT), prostaglandins and numerous cytokines. Mast cells carry adenosine A2b receptors and adenosine can trigger an asthmatic response in sensitive individuals. CV Therapeutics is investigating an oral adenosine antagonist (CVT-6883) in Phase 1 trials which may be able to modulate such a response, blocking release of further inflammatory molecules.

Another approach involves inhibiting an enzyme inside mast cells called Syk kinase, preventing signal molecules from triggering a subsequent release of inflammatory factors. Rigel Pharmaceuticals has developed an inhaled small molecule Syk kinase inhibitor (R343) and Pfizer will now take the compound into clinical trials.

Probably acting even earlier in the process, Avanir Pharma's AVP 13358 targets IgE, preventing it from initiating the cascade of inflammatory mediators. This compound, now in Phase 1, also appears to inhibit the release of various cytokines, such as IL-4 and IL-5.

3. Antihistamines (Fig.2, arrow 3):
One cause of constriction of the airways in acute allergic asthma is the release of histamine from sensitised mast cells. Therapy with antihistamines is successful in such cases and already well established. UCB has a new antihistamine, efletirizine, in development for allergic rhinitis and this compound has completed Phase 1 studies.

4. The blockade of other inflammatory molecules (Fig. 2, arrow 4):
In this category are human antibodies or other compounds designed to block some of the receptors to which cytokines or other inflammatory molecules bind, or which neutralise them directly. GSK has a monoclonal antibody (mepolizumab) in Phase 2 trial and Wyeth's etanercept is at the same stage. AstraZeneca's CAT-354 is directed against the cytokine IL-13 and is in Phase 1 trial, as is Amgen's AMG 317, which acts against IL-13 and IL-4. Aerovance has AER-001 that can be inhaled and which binds to IL-4 and IL-13 receptors, blocking inflammation. It is in Phase 2 development. MediciNova, meanwhile, has an orally administered inflammatory inhibitor (MN-001) in Phase 2 trial.

5. Agents blocking the action of neuropeptides (Fig.2, arrow 5):
Neuropeptides are small molecules that act as neurotransmitters. They are produced in the brain but can be released at nerve endings, where they cause inflammation and contraction of smooth muscle, including that in the airways. The possibility that compounds that block neurokinin (NK) receptors might be beneficial in asthma is being explored by Daiichi-Sankyo, whose compound CS-003 is in Phase 2 trial.

6. Agents which open the airways in the lungs (bronchodilators) (Fig. 2, arrow 6):
Although they have long been the established therapies, there are a large number of new bronchodilators and steroid anti-inflammatory compounds (and combinations of both) in clinical development. GlaxoSmithKline has five new long-acting bronchodilators in Phase 2 trials (GSK 159797, 159802, 597901, 642444 and 678007), either singly or in combination with a glucocorticoid agonist, and three new glucocorticoid agonists - (GSK 685698, 870086 and 799943) at Phase 2. In addition, Trinity-Chiesi has a new long-acting beta$_2$-agonist

Figure 3: **House dust mite - a common cause of asthma**

(carmoterol) in Phase 2 development. New steroids under study include the inhaled corticosteroid QAE 397 (Novartis) and the non-glucocorticoid EPI-12323 from Epigenesis, both at Phase 2. Among combination products under development, Novartis has a combination of formoterol and mometasone (MMF 258) in Phase 3 and sanofi-aventis is developing a combination of formoterol and ciclesonide, which has reached Phase 2.

Asthma research is an area of intense activity, building on a growing understanding of the complex processes involved in both acute attacks and the development of chronic asthma. Many new compounds can also be expected to have value in the management of chronic obstructive pulmonary disease (COPD), which shares many inflammatory features with allergic asthma. More needs to be done to understand and counteract the various environmental triggers thought to promote asthma if the current trend towards an increasing burden of disease is to be reversed.

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British Lung Foundation,
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Website: www.lunguk.org

ATHEROSCLEROSIS

What is atherosclerosis?

Also called arteriosclerosis, this is an inflammatory process leading to a degeneration of the artery wall. In its early stages, fatty deposits (plaques) form just under the surface layer of cells lining the artery wall, causing thickening of the walls and restricting blood flow (Figure 1). Later, blood clots can form, further reducing blood flow and increasing the risk of embolism.

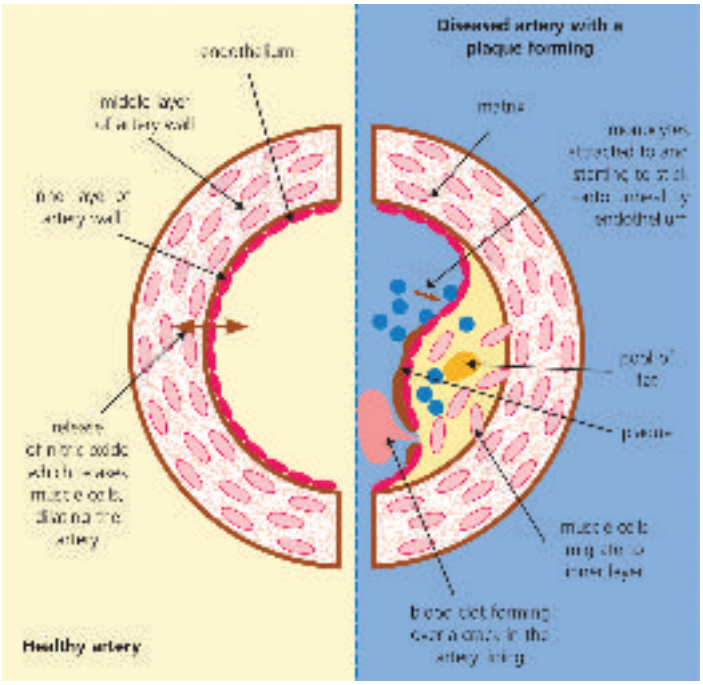

Figure 1: **Diagrammatic cross section of a healthy and an atherosclerotic artery**

Plaque in the coronary artery will predispose people to angina pains and heart attack (see *Ischaemic Heart Disease*), while plaque in the neck and head increases the risk of dementia and ischaemic stroke (see *Stroke*). Plaque can also form in the arteries supplying the limbs (see *Peripheral Vascular Disease*). Plaques increase resistance to blood flow, forcing the heart to work harder, contributing to hypertension (raised blood pressure) and heart failure. They also reduce delivery of oxygen to vital organs, causing angina or pain on walking (see *Peripheral Vascular Disease*), and act as sites for blood clots which may detach and cause acute embolism (see *Thrombosis*). Atherosclerosis may thus be seen as a central feature of many of the main circulatory diseases (Figure 2), and treating it can be expected to reduce the risks of these diseases.

Many factors contribute to the formation of atherosclerotic plaque. It is known that age and family history (inheritance) are important risk factors, as is obesity. In addition, plaque formation is most probably a response to injury to the arterial wall by excess

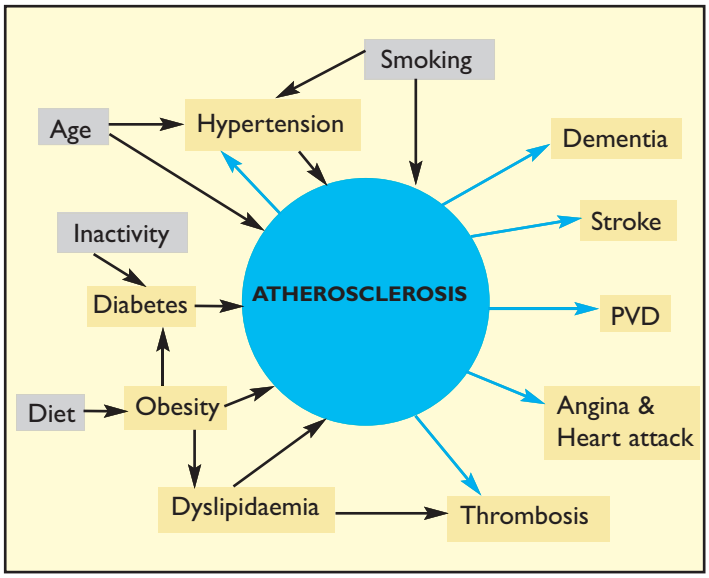

Figure 2: **Atherosclerosis stands at the centre of a web of circulatory and metabolic diseases**

cholesterol, chemicals in cigarette smoke, raised blood pressure and chemical changes induced by diabetes.

Who does atherosclerosis affect?

The blockage of blood vessels by plaque or blood clots is a major cause of illness and death in the UK, where cardiovascular disease accounts for a large number of deaths. Plaque formation starts very early in life. Signs of it (called 'fatty streaks') are found even in the main arteries of three-year-olds, and 77 per cent of soldiers killed in battle (at an average age of 22) had extensive plaques. So it would appear that plaque occurs in all of us, but it is the degree and rate of formation that are important.

Present treatments and shortcomings

A healthy lifestyle will help control plaque formation - as will the treatment of related conditions (see *Hypertension* and *Diabetes*). Cholesterol and triglyceride levels can be controlled by dietary measures, but some people have difficulty keeping to such diets, or have an inherited tendency towards high levels of blood

NEW SINCE 2000

2003 - Rosuvastatin (Crestor, AstraZeneca)

2003 - Ezetimibe (Ezetrol, Merck Sharp & Dohme, Schering-Plough)

2005 - Ezetimibe + Simvastatin (Inegy, MSD & S-Plough)

cholesterol, and require active therapy. The main classes of medication to control cholesterol level are **bile acid sequestrants, fibrates, nicotinic acid derivatives** and **statins**. In addition, omega-3 triglycerides (e.g. Omacor, Solvay) reduce cholesterol and triglyceride levels, as do nicotinic acid derivatives. More recently, a selective cholesterol absorption inhibitor, ezetimibe, (Ezetrol, Merck Sharp & Dohme and Schering-Plough) has been introduced that reduces cholesterol absorption from the intestine. Ezetimibe can be used alone, but is more often taken together with a statin, when it has an additive effect on lowering cholesterol, and a fixed combination product that combines it with simvastatin (Inegy, Merck Sharp & Dohme and Schering-Plough) is also available.

Bile acid sequestrants have been available for almost 30 years. They work by binding to and removing bile acids (which are made from cholesterol) from the gut during digestion. As the body produces more bile acids, cholesterol in the blood is consumed and a fall of 15-30 per cent may be achieved. However, absorption of fat-soluble vitamins (A, D, K) is also reduced and circulating levels of many other medicines given at the same time can be affected.

Nicotinic acid is a water soluble vitamin B complex which may work by decreasing free fatty acid release from adipose tissue. Nicotinic acid increases HDL by 30 per cent and reduces triglycerides by 27 per cent. It is used in conjunction with statins to treat dyslipidaemia, particularly in patients with elevated LDL and triglycerides and low HDL. Nicotinic acid derivatives can induce flushing that may limit their use. A prolonged release version of nicotinic acid (Niaspan, Merck Pharmaceuticals) has been introduced that reduces these flushing events.

The **fibrates** (e.g. fenofibrate, bezafibrate, gemfibrozil) appear to act by altering the lipid balance in the blood. Over a period of time, a 5-15 per cent reduction in cholesterol level has been demonstrated. Fibrates are used to treat at-risk men whose hyperlipidaemia - an abnormally high level of fat in the blood or tissues - is resistant to diet and other medication. They can cause a muscle-wasting condition called rhabdomyelitis, and people using this medicine need to be regularly monitored to detect its onset.

The most-used medicines are the **statins**. These block a key step in the formation of cholesterol, reducing its level by 30 per cent or more and helping to improve triglyceride levels as well. They include atorvastatin (Lipitor, Pfizer), fluvastatin (Lescol, Novartis), pravastatin (Lipostat, Bristol-Myers Squibb), simvastatin (Zocor, Merck Sharp & Dohme) and rosuvastatin (Crestor, AstraZeneca). Statins confer significant benefits beyond their main indications, such as reducing the risks of dementia, strokes or a second heart attack. It has been demonstrated that, in high dose, rosuvastatin is even able to reverse the build-up of atherosclerotic plaque in the coronary arteries. However, this highly desirable result was seen at a dose above that normally used and no statin is currently available for the reversal of established atherosclerosis. Statins are generally well tolerated, but rare cases of rhabdomyelitis have been reported, as with fibrates.

What's in the development pipeline?

Compounds in development exploit a very wide range of approaches to regulating lipid levels and preventing atherosclerosis, reflecting the numerous processes involved. Some seek to improve existing approaches, such as Takeda's TAK-475, currently in Phase 3 trial, which inhibits a later stage from statins in the production of cholesterol. Others, such sanofi-aventis's rimonabant, also in Phase 3 trial, seek to exploit quite new pathways.

1. Combination products
Increasingly, treatments are aimed at bringing about three key changes in blood lipids: reducing 'bad' low-density lipoprotein (LDL)-bound cholesterol, increasing 'good' high-density lipoprotein

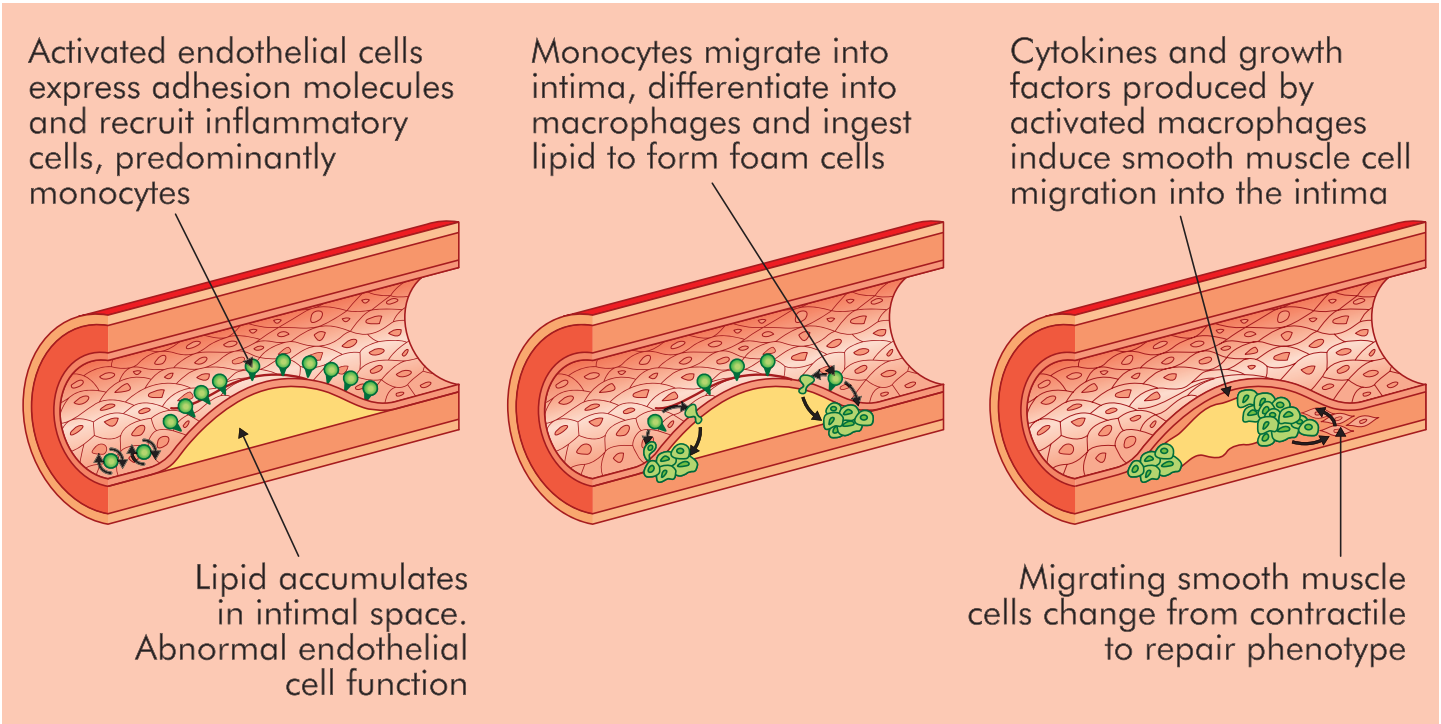

Figure 3: **Early stages in the formation of atherosclerotic plaque**
Reprinted from Davidson's Principles and Practice of Medicine

(HDL)-cholesterol, and normalising circulating triglycerides. This may often mean combining two or more agents, or developing compounds with multiple activities. Thus, Merck Sharp & Dohme is developing a combination (MK-0524B) of simvastatin, niacin and a third agent designed to prevent the blushing often provoked by niacin.

2. Intestinal cholesterol blockers
Inhibitors of the enzyme acyl-CoA:cholesterol acyltransferase (ACAT inhibitors) reduce absorption of cholesterol from the intestine, but work in a different way from that of ezetimibe. Kowa has the compound K-604 in Phase 1 and also has a new 'superstatin' compound, pitavastatin (NK104), in Phase 3 trial. Sanofi-aventis has the cholesterol absorption inhibitor AVE 5530 at Phase 2.

3. Inhibitors of plaque formation
GlaxoSmithKline's compound SB 480848 (darapladib), currently in Phase 3 trial, is an example of a new approach that tries to block plaque formation. The company has two other inhibitors (GSK 659032, rilapladib and GSK 568859) at Phase 1, as a back-up to darapladib.

Blocking inflammatory cell recruitment, and thus plaque formation, is also thought to explain the activity of AGI-1067, a compound in Phase 3 trial being developed by AstraZeneca and AtheroGenics.

4. Agents that affect HDL-cholesterol levels
Research is especially active into agents that can raise the level of 'good' HDL-cholesterol, which has a protective effect against the progression of atherosclerosis. These make up three distinct groups: cholesteryl ester transfer protein (CETP) inhibitors, so-called PPAR modulators, and substances similar to an HDL component known as apolipoprotein A-1.

Several companies have **CETP inhibitors** in development. Roche's R1658 has reached Phase 2, as has MK-0859 from Merck Sharp & Dohme, while Bayer's BAY 60-5521 and Japan Tobacco's JTT-302 are at Phase 1.

Peroxisome Proliferator-Activated Receptors (PPARs) are 'master switches' that regulate a variety of important processes in the body, including the formation and breakdown of lipids. Three types are known: PPAR alpha, gamma and delta. PPAR-gamma activators (glitazones) are used to treat diabetes, and it was noted that lipid imbalances often seen in diabetes were improved by this treatment. Further interest was aroused by the discovery that fibrates, which have long been known to raise HDL-cholesterol levels, are PPAR-alpha activators. This has encouraged several companies to develop new medicines from this area of research.

Those in Phase 2 study are:

- PPAR-alpha activators from Kyorin (KRP 101) and sanofi-aventis (AVE 8134)
- Dual PPAR-alpha/gamma activators, including: LBM 642 (Novartis), AVE 0847 (sanofi-aventis) and AZD 6610 (AstraZeneca)
- A PPAR-delta activator (GSK 501516) from GlaxoSmithKline.

The other major new line of research into ways of preventing atherosclerosis explores variants of **apolipoprotein A-1**, a normal constituent of HDL. A genetic study found that a small number of people living by Lake Garda in northern Italy had very low levels of HDL-cholesterol but also a very low risk of having cardiovascular disease. Investigations showed that these people had inherited a variant form of apolipoprotein A-1 that was very effective at clearing cholesterol from artery walls and other tissues (thus shrinking atherosclerotic plaques) and transporting it back to the liver for elimination. This finding encouraged development of a form of the protein combined with phospholipid to mimic natural HDL and Pfizer now has this agent (ETC-216), which is given by injection, in Phase 2 trial. Data have shown that this synthetic form of HDL is able to reduce plaque size in coronary arteries. Novartis is also exploring this approach and the company is developing an oral form of an Apo A-1 'mimic' (APP 018) that is in Phase 1 trial.

The longer-term future

The processes behind atherosclerosis are so closely linked with those of other major diseases that advances in treating this condition will have enormous health benefits. Many other projects than those above have promise in this area, and other pathways may eventually turn out to be important too. However, such is the intensity of research in this area that the outlook for new treatments becoming available over the next ten years is surely bright.

FOR FURTHER INFORMATION CONTACT:

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BACTERIAL INFECTIONS

What are bacterial infections?

Bacteria are microscopic organisms of many different types with a chemically distinctive cell wall. This gives each type a particular shape - spherical, rod-shaped or spiral. They multiply by cell division - a process that can occur every 20-30 minutes. A single bacterium entering the body and multiplying at this rate could give rise to over 30 billion new cells within 12 hours. Fortunately, most bacteria are harmless and some are even essential, such as those in the intestine which aid digestion. But a minority, called *pathogens*, cause disease (Figure 1 and Table 1). These may be localised near the surface of the skin, as in laryngitis, boils and abscesses, or invade internal organs and cause, for example, infections of the digestive or urinary tract, brain (meningitis), lung (pneumonia), heart (endocarditis), or the bloodstream (sepsis), which can be serious or life-threatening.

Who do bacterial infections affect?

Everyone experiences bacterial infections from time to time, but most infections heal by themselves or are readily treated with antibiotics. However, resistance to antibiotics is an ever-growing problem and infections that were easily treatable a decade ago are now staging a come-back in deadlier form.

People whose immunity is depressed by other illnesses such as cancer, or by immunosuppressive treatments, as in transplant

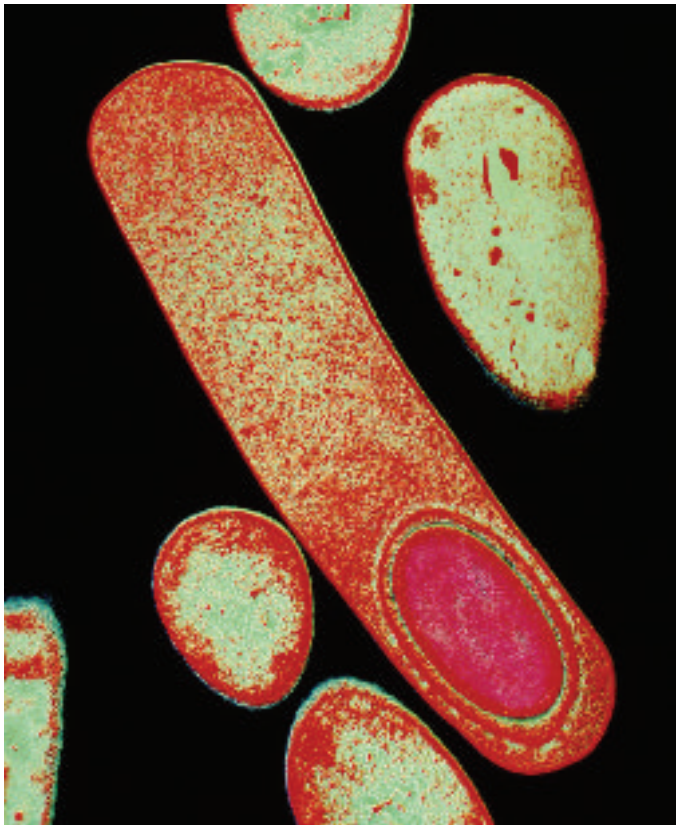

***Figure 1: Clostridium difficile* is a bacterium that causes antibiotic-associated diarrhoea. It is difficult to eliminate, as it produces spores that survive outside the body.**

Examples of bacteria and some related illnesses*

GRAM-POSITIVE		GRAM-NEGATIVE	
Staphylococcus aureus	MRSA blood poisoning	Neisseria meningitidis	Meningitis
Streptococcus pneumoniae	Pneumonia	Moraxella catarrhalis	Sinusitis, bronchitis
Streptococcus pyogenes	Necrotising fasciitis	Bordetella pertussis	Whooping-cough
Enterococcus spp	Bacteraemia	Escherichia coli	Peritonitis, sepsis
Clostridium difficile	Diarrhoea	Klebsiella pneumoniae	Pneumonia, urinary-tract infections
Bacillus anthracis	Anthrax	Salmonella typhi	Typhoid fever
Listeria monocytogenes	Listeriosis	Pseudomonas aeruginosa	Burn/wound infections
NOT RELIABLY STAINED BY GRAM'S METHOD			
	Borrellia burgdorferi		Lyme disease
	Legionella pneumophila		Legionnaires' disease
	Mycobacterium tuberculosis		Tuberculosis
	Mycobacterium leprae		Leprosy
	Treponema pallidum		Syphilis
	Rickettsia rickettsii		Rocky Mountain spotted fever

* Note: This listing of bacteria and diseases is not exhaustive

***Table 1:* Bacteria are often distinguished according to whether they are stained by a method first described in 1884 by the Danish bacteriologist Hans Christian Gram.**

surgery, are at greater risk of serious infection. Hospital-acquired infections are becoming increasingly frequent. If an infection (sepsis) develops, it may lead to septic shock - a cascade of inflammation, blood clotting and low blood pressure that often results in death through multiple organ failure. In 2004, people with sepsis required over 270,000 bed-days of inpatient care in hospitals in England and sepsis was recorded as the underlying cause of more than 2,000 deaths in England and Wales, 87 per cent of them in people aged 60 and over. During the same period there were more than 7,000 cases of bacteria in the blood due to methicillin-resistant *Staphylococcus aureus* (MRSA) in England and more than 44,000 infections due to *Clostridium difficile*, with over 1,200 deaths due to this organism. A study has shown that the cost of treating patients who develop sepsis after admission to an intensive care unit exceeded £10,000 per patient (in 1999).

NEW SINCE 2000

2001 - Linezolid (Zyvox, Pfizer)
2001 - Telithromycin (Ketek, sanofi-aventis)
2002 - Ertapenem (Invanz, Merck Sharp & Dohme)
2002 - Drotrecogin (Xigris, Lilly)
2003 - Moxifloxacin (Avelox, Bayer)
2006 - Tigecycline (Tigacyl, Wyeth)

Class	Mode of action	Examples	
Beta-lactams	Inhibit bacterial cell wall synthesis	Penicillins	Penicillin G Amoxicillin Piperacillin
		Cephalosporins	Cefalexin Cefuroxime Ceftazidime Ceftriaxone
		Carbapenems	Ertapenem Meropenem
Glycopeptides	Inhibit cell wall synthesis & assembly	Vancomycin Teicoplanin	
Quinolones	Inhibit bacterial DNA replication	Ciprofloxacin Norfloxacin Moxifloxacin	
Aminoglycosides	Inhibit bacterial protein synthesis by binding to 30S ribosomal subunit	Amikacin Gentamicin Netilmicin Tobramycin	
Macrolides	Inhibit bacterial protein synthesis by binding to 50S ribosomal subunit	Erythromycin Azithromycin Clarithromycin	
Ketolides	Inhibit bacterial protein synthesis	Telithromycin	
Tetracyclines and derivatives	Inhibit bacterial protein synthesis by blocking tRNA binding to ribosomes	Doxycycline Chlortetracycline Tigecycline	
Oxazolidinones	Inhibit bacterial protein synthesis	Linezolid	
Streptogramins	Inhibit bacterial protein synthesis	Synercid	
Sulphonamides	Inhibit folate synthesis	Sulfamethoxazole Trimethoprim	
Others	Various	Chloramphenicol Metronidazole Aztreonam Clindamycin Rifampicin	

Table 2: **Some major types of antibiotics currently available and their mechanisms of action.**

Their average stay in the unit was 16 days, compared with 2 days for those without sepsis, and their death rate 50-60 per cent (versus 20 per cent).

Present treatments and shortcomings

Many antibiotics have been discovered over the last fifty years, including the penicillins and cephalosporins, tetracyclines, macrolides, aminoglycosides (streptomycin group) and quinolones. (Table 2) Despite this range of medicines, the emergence of resistant organisms such as MRSA and vancomycin-resistant enterococci (VRE) is creating widespread concern.

A variety of antibiotics have been introduced in recent years, in an attempt to keep ahead of growing resistance. Synercid (quinupristin/dalfopristin, sanofi-aventis), the first of the streptogramin group, combines two components that together kill a wide range of bacteria, including MRSA strains. Linezolid (Zyvox, Pfizer) is an oxazolidinone which is used in hospital for treating pneumonia and skin and soft tissue infections due to resistant strains of Gram-positive bacteria. Another new class of antibiotic (ketolides), is represented by telithromycin (Ketek, sanofi-aventis). It is used to treat community-acquired respiratory tract infections, including those caused by resistant strains of *Streptococcus pneumoniae*. More recently, tigecycline (Tygacil, Wyeth) has become available for the treatment of complicated skin, soft tissue and intra-abdominal infections and Novartis has daptomycin (Cubicin) for the first two of these uses.

What's in the development pipeline?

The search continues for antibiotics that work in new ways, and so might be active against bacteria that have developed resistance to other medicines. GlaxoSmithKline has completed Phase 3 trials for retapamulin, the first in the class of pleuromutilin antibiotics, and two further members of this class (GSK 565154 and 742510) are in Phase 1 development. Retapamulin is applied to the skin (a *topical* medicine) in skin and soft tissue infections. Merck Sharp & Dohme's platensimycin blocks enzymes involved in fatty acid production that are used by bacteria to make their cell walls. It is still in early development, but pre-clinical experiments have shown it to be effective against MRSA and vancomycin-resistant enterococci, two key types of antibiotic-resistant bacteria.

Many new members of existing classes of antibiotics are also in development:

- A second **ketolide** antibiotic (cethromycin, Advanced Life Sciences) is in Phase 3 study for community-acquired pneumonia.
- Replidyne is developing the oral **penem** (faropenem medoxomil, Orapem) and Johnson & Johnson is conducting Phase 3 trials of doripenem in urinary tract infections, intra-abdominal infections and hospital-acquired pneumonia. Roche is also developing a new carbapenem - R1558, which has reached Phase 2 trials.
- Pfizer is investigating dalbavancin (Zeven), a **lipoglycopeptide** in the same class as vancomycin. Dalbavancin can be given once weekly, and is active against Gram-positive but not Gram-negative bacteria. Another lipoglycopeptide in development is telavancin (Theravance), which has reached Phase 3 trials in hospital-acquired pneumonia and complicated skin and skin structure infections.
- Other new antibiotics under development for skin infections include Arpida's Iclaprim, a **dihydrofolate reductase inhibitor** in the trimethoprim class, which is in Phase 3 trials as an injectable and at Phase 1 in oral form.
- Two new **cephalosporins** are under investigation: ceftobiprole (Basilea, Phase 3) and ceftaroline acetate (Cerexa, Phase 2).
- In addition, Enanta is investigating a new **macrolide** (EDP-420) in Phase 2 trials for community acquired pneumonia.
- Sanofi-aventis has a new oral **streptogramin** (XRP 2868) at Phase 1, as has Novexel (NXL 103).
- New **quinolone** antibiotics are also still being developed. Oscient Pharmaceuticals has gemifloxacin (Factive) in Phase 3 trial for bacterial sinusitis, while Schering-Plough has the broad-spectrum agent garenoxacin. Daiichi-Sankyo has the injected fluoroquinolone DU-6859a (sitafloxacin) in Phase 2 trials and is preparing Phase 3 trials for the oral form of this medicine. The company also has the quinolone DX 619 in Phase 1 trial.

Of particular interest are new treatments for the serious problem of C. *difficile* diarrhoea, for which metronidazole and vancomycin are the only currently available antibiotics. Two new antibiotics under development are ramoplanin, a lipoglycopeptide being studied by Oscient that acts to kill the bacteria in the intestine, and Tiacumicin B, being tested by Par Pharmaceuticals. Both have reached Phase 2 trials. Genzyme is working on a new approach that uses a non-absorbed polymer (tolevamer) to bind the toxins released by this organism and hence control the diarrhoea associated with its uncontrolled growth in the intestine. Tolevamer is now in Phase 3 trials. Another toxin-binding approach is being explored by Medarex in Phase 2 trials of MDX-066, a monoclonal antibody against *C. difficile*.

The remaining big problem in bacterial infection, apart from antibiotic resistance, is the lack of effective medicines for treating **severe sepsis**, which still causes a lot of deaths. Drotrecogin alfa activated (Xigris, Lilly), a version of the naturally occurring activated Protein C, has been introduced, but the reduction in death rate it brings is relatively modest and new alternatives are urgently needed. A major challenge to developing effective therapies is the great complexity of inflammatory and blood-clotting pathways that are activated in sepsis, making it difficult to find an agent that can shut down the cascade of events that lead to circulatory collapse and organ failure.

Eisai has a compound (E5564, eritoran) in Phase 3 trial that may offer an alternative, as it inhibits an early step in the events leading to the rapid production of inflammatory cytokines involved in sepsis. A Phase 3 study of this compound has now started to evaluate whether eritoran can significantly lower the death rate from severe sepsis. Takeda also has a TLR-4 inhibitor (TAK-242) under investigation and Novartis is investigating TFP 561 (tifacogin, Phase 3) in severe community acquired pneumonia, which may precede sepsis. Meanwhile, AstraZeneca is preparing a Phase 3 trial of the antibody CytoFab which is directed against TNF-α (one of the key inflammatory cytokines). If any of these compounds can be shown to produce a substantial decrease in sepsis-associated deaths, that will be a very welcome development for those clinicians and patients facing the most dramatic forms of bacterial infection.

B

BENIGN PROSTATIC HYPERPLASIA

What is benign prostatic hyperplasia?

Benign prostatic hyperplasia (BPH), is a non-cancerous enlargement of the prostate gland, constricting the tube leading from the bladder (urethra), making the passing of urine difficult. Its development is linked to an age-related decrease in male hormones.

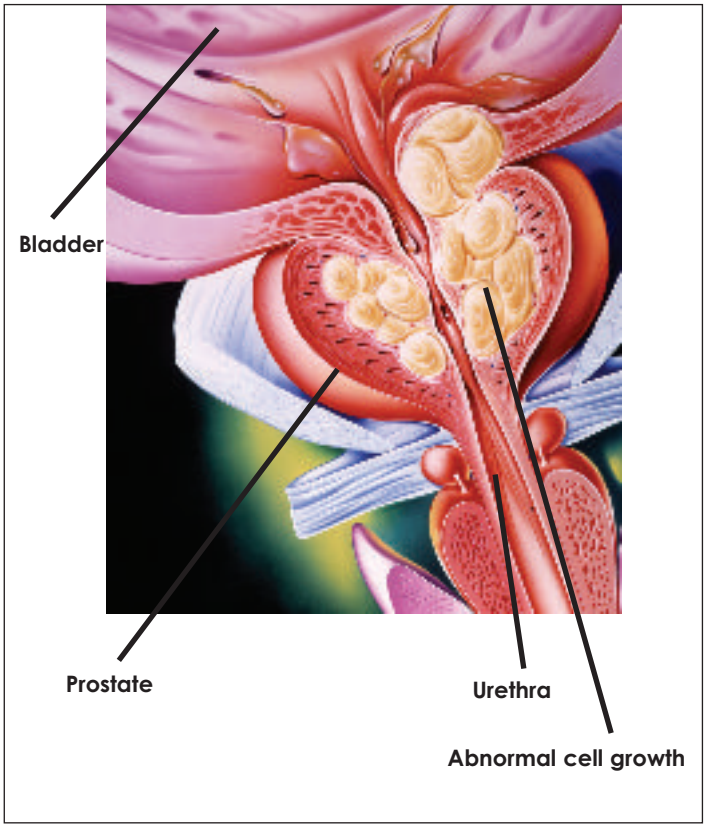

Figure 1: **A growth of cells leads to constriction of the urethra where it passes through the prostate, reducing urine flow.**

Who does BPH affect?

Benign prostatic hyperplasia is the commonest cause of urination difficulties in men. Some prostate enlargement is apparent in 75 per cent of men over 50. However, prostate enlargement does not always give rise to symptoms and, even when it does, only about half of those affected seek medical help. Estimates of the number affected have varied in different surveys. Depending on definitions used, clinical signs may be apparent in 15-30 per cent of individuals in their 60s.

Present treatments and shortcomings

Several medicines are available that can control symptoms in the earlier stages of BPH, although surgical intervention may eventually become necessary. The most used are the alpha-adrenoceptor antagonists, which block receptors in the muscles that control emptying of the bladder, improving urine flow.

NEW SINCE 2000

2001 - Doxazosin (Cardura, Pfizer)

2003 - Dutasteride (Avodart, GSK)

2005 - Alfuzosin (Xatral, sanofi-aventis)

2005 - Tamsulosin (Flomaxtra XL, Astellas)

Selective alpha-adrenoceptor blockers now launched in the UK are: alfuzosin (Xatral, sanofi-aventis), doxazosin (Cardura, Pfizer), indoramin (Doralese, Glaxo¬SmithKline), prazosin (Hypovase, Pfizer), tamsulosin (Flomaxtra XL, Astellas), and terazosin (Hytrin, Abbott). These compounds are generally well tolerated, although some may cause dizziness or interfere with blood pressure control.

Relieving the symptoms, though, does not deal with an enlarging prostate. For this purpose, Merck Sharp & Dohme introduced finasteride (Proscar), the first compound to inhibit the enzyme 5-alpha-reductase that converts the male sex hormone testosterone into the more potent dihydrotestosterone (DHT) which induces prostate enlargement. Inhibiting this enzyme reduces DHT formation and, as a result, shrinks the enlarged prostate gland. However, six months or more of use is often necessary before its full effectiveness can be judged; in addition, decreased libido and impotence may occur.

Another 5-alpha reductase inhibitor is GlaxoSmithKline's dutasteride. This inhibits both type 1 and type 2 5-alpha-reductase enzymes (finasteride inhibits only type 2), giving a particularly marked suppression of DHT formation.

What's in the development pipeline?

Development of new alpha-adrenoceptor blockers continues. Silodosin from Kissei, which targets alpha receptors, is in Phase 2. In addition, GlaxoSmithKline is testing a fixed combination of dutasteride and an alpha-blocker (GI-198745) in Phase 3 trials and sanofi-aventis's alfuzosin aims to prevent acute urinary retention (a complication of benign prostatic hyperplasia that requires emergency treatment).

No new 5-alpha reductase inhibitors are currently in development, but a variety of other approaches is being tried. Vitamin D3 (calcitriol) is thought to be able to reduce cell proliferation in the prostate, like 5-alpha reductase inhibitors. However, the vitamin itself is not suitable for use as a treatment, because of its effects on the way calcium and phosphate are processed by the body. Instead, versions that do not induce excessive calcium levels have been developed; BioXell has a compound (BXL-628) in Phase 2 trial. Also at this stage, Eli Lilly and ICOS are studying tadalafil (Cialis). This compound may cause relaxation of the smooth muscle within an enlarged prostate, thereby easing urine flow.

Nymox Pharma also has a compound (NX-1207) in Phase 2 trial. Finally, some other hormonal approaches are being tried. Ardana Biosciences has a gonadotrophin releasing hormone antagonist (Teverelix) that reduces testosterone and dihydrotestosterone levels and has shown improvements in symptoms in a Phase 2 trial and Aeterna Zentaris has two Luteinizing Hormone Releasing Hormone antagonists in trial (Ozarelix, Phase 2, and Cetrorelix, Phase 3).

The longer-term future

Several effective medicines are now available for the treatment of the symptoms of benign prostatic hyperplasia and successful research continues into new approaches. Further research into the biology of the prostate and its growth regulation are also needed to further improve management of benign prostatic hyperplasia - a condition that is likely to become even more common with the 'greying' of Britain's population over the next two decades.

FOR FURTHER INFORMATION CONTACT:

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B

BIPOLAR DISORDER

What is bipolar disorder?

Formerly known as manic depression, bipolar disorder is a condition involving severe mood swings, from periods of elation and agitation (mania) to episodes of profound depression. Psychotic symptoms (hallucinations, delusions) are common, as is anxiety. Episodes of depression are usually more common than episodes of mania, and bipolar disorder is often misdiagnosed as unipolar depression (see *Depression*), at least initially. This may have serious consequences, as antidepressant treatment by itself may provoke an episode of mania.

Mania typically results in severe disturbance of normal life and relationships. A less severe form (hypomania) may occur instead that does not cause major functional impairment. A distinction is often made between bipolar I disorder (mania + depression) and bipolar II disorder (hypomania + depression), but treatment is required in both cases. In this section, the term bipolar disorder refers to the more serious bipolar I disorder, unless stated otherwise.

The course of bipolar disorder is very variable. Some people with bipolar disorder experience more than four episodes of mania or hypomania or depression in a year, which is known as rapid cycling. Others may have extended periods of normal mood (*remission*) between episodes. Bipolar disorder is more likely than unipolar depression to require referral for specialist, hospital-based treatment, and manic episodes in particular are a prominent cause of hospital admission.

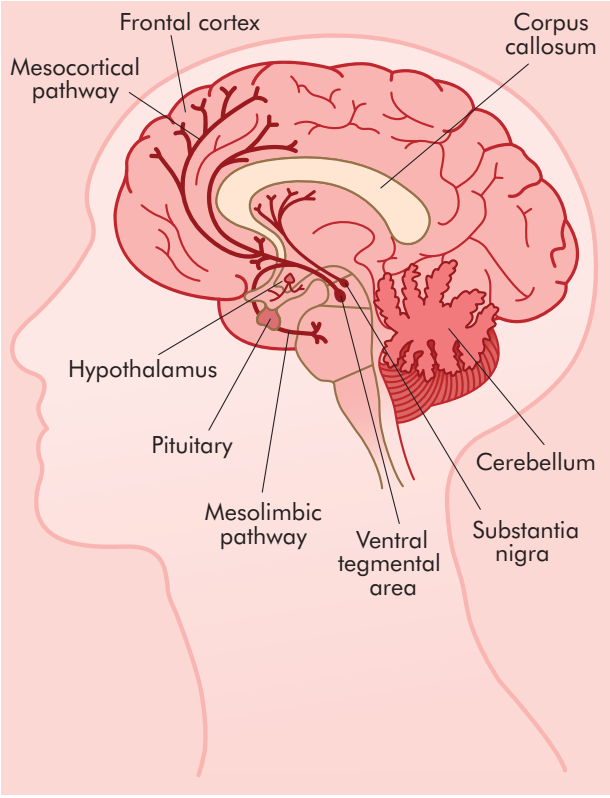

Figure 1: **Dopaminergic neurotransmission in the brain is thought to be affected in bipolar disorder. (DA-containing neuronal projections are shown in red)**

The causes of bipolar disorder, like those of depression and anxiety, are not well established. There is clear evidence that the disorder runs in families, but inheritance is not simple and there are likely to be many genes that contribute to susceptibility. Major life events and childhood trauma/abuse, which are thought to be important predisposing factors in unipolar depression, appear to play a smaller role in bipolar disorder. Abnormalities in levels of neurotransmitters in the brain are important, as in unipolar depression, although it is thought that the neurotransmitter dopamine is likely to be most involved in bipolar disorder, rather than noradrenaline or serotonin levels.

Who does bipolar disorder affect?

Bipolar disorder is less common than unipolar depression and is thought to affect about 0.5 per cent of the population over the course of a lifetime. Onset of symptoms usually occurs slightly earlier than in depression, peaking between the ages of about 15-25 years. Its prevalence appears to be about the same in men and women.

Present treatments and shortcomings

The treatments currently authorised in the UK for the treatment of acute mania are lithium salts and semisodium valproate (Depakote, sanofi-aventis). A further medicine may be added if response to lithium is insufficient. Those most often used are olanzapine (Zyprexa, Lilly), quetiapine (Seroquel, AstraZeneca) and risperidone (Risperdal, Janssen-Cilag). Lithium, valproate and olanzapine are also used for long-term prevention of recurrence after a manic episode. If these are not sufficient, the anti-epilepsy medicines carbamazepine (Tegretol, Novartis) or lamotrigine (Lamictal, GSK) may sometimes used, although the latter is not currently authorised for this purpose.

Episodes of depression in bipolar disorder are treated using antidepressants, and a selective serotonin reuptake inhibitor (SSRI; (see *Depression*) is recommended initially. However, it is important that an anti-manic medication should be given at the same time, to avoid the risk of switching into an episode of mania, or accelerating the rate of cycling, which may happen if antidepressants are used alone. For similar reasons, the antidepressant is usually discontinued after resolution of the depressive episode and not continued long-term.

Tremor, sedation, dizziness, weight gain, nausea and other gastrointestinal symptoms are among the most common adverse effects experienced during treatment with the main anti-manic medications. These may be troublesome enough to limit the dose that can be given or to make some people stop taking their medication. Sudden stopping (or erratic use) of lithium, for example, may result in a recurrence of mania. Weight gain may increase the risk of developing diabetes, or may worsen pre-existing diabetes. For such reasons, newer medications with fewer and milder side-effects would be desirable for the management of bipolar disorder.

Following resolution of an acute episode, some forms of psychological therapy may also be helpful in addition to the use of medication. Psychosocial support (befriending) and participation in self-help groups may also be appropriate.

What's in the development pipeline?

Advanced projects for developing new treatments for bipolar disorder largely involve extensions to uses of existing medications. For example, quetiapine (Seroquel, AstraZeneca) is already available for the treatment of acute mania, and is now in Phase 3 study for use in managing acute depressive episodes and for the maintenance of remission. A sustained release formulation is also in Phase 3 trials. Risperidone and topiramate (Topamax, Janssen-Cilag) are also undergoing Phase 3 studies that would broaden their uses. In addition, Lilly is studying a new combination (Symbyax) of olanzapine and the SSRI fluoxetine in bipolar depression. While these initiatives may be seen to some extent as a verification of existing practice, they are nonetheless important for putting treatment on a more secure basis, as bipolar disorder has been less extensively studied in the past than unipolar depression.

New compounds in development include licarbazepine (Novartis), which is in Phase 3 trial for acute mania, an extended release form of paliperidone (Johnson & Johnson), a derivative of risperidone, also in Phase 3 trial, an oral form of uridine (RG2417) and triacetyluridine (RG2133, RepliGen), in Phase 2 trial, and, at Phase 1, a derivative of valproate (DP-VPA, D-Pharm) which has been developed to have a better side-effect profile than valproate itself. In addition, Forest Labs has RGH-188 at the same stage, and Memory Pharma is testing MEM 1003 (Phase 2) for control of acute mania.

FOR FURTHER INFORMATION CONTACT:

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CANCER

What is cancer?

Cancer is a disorder in which there is unregulated multiplication of cells in the body. The resulting cell mass, called a tumour, may eventually develop its own blood system (Figure 1) and begin to invade neighbouring organs. Some cancers, known as 'malignant', shed cells into the blood or lymph and these cells become trapped in small blood vessels in organs such as the liver, lung or brain, where they form secondary tumours called *metastases*. Metastatic disease cannot be cured. In late disease, tumours release substances that depress appetite and cause weight loss and often lead to death from overwhelming infection, such as pneumonia. This section considers research on medical treatments for solid tumours (see *Leukaemia* for research on blood cancers).

Tumours can develop in any organ. Depending on where they arise, they pose very different medical and management problems. Some can be treated medically, but many are hard to cure except through surgical or radiological treatment. However, advances in medical research have made many more treatable, and today many of those who have cancer live longer than previously, and with a better quality of life.

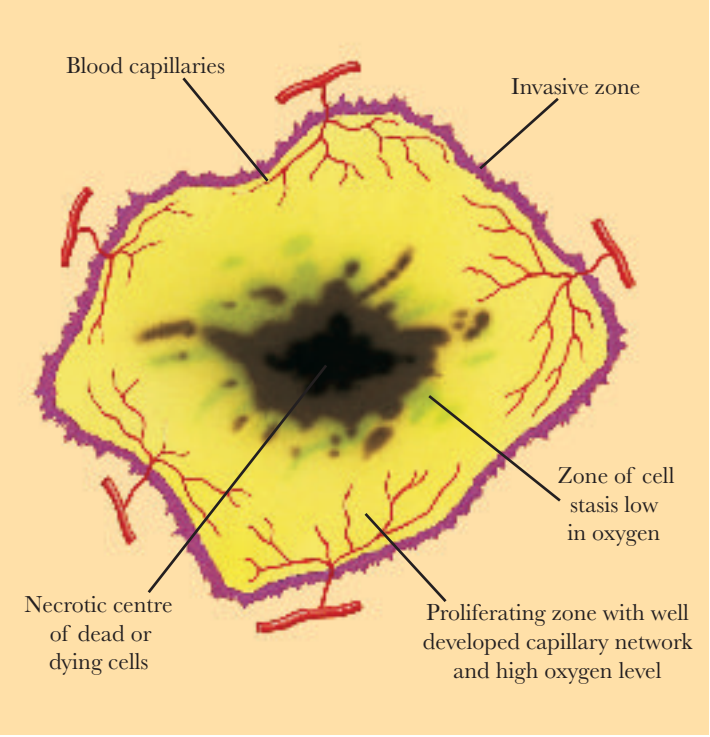

Figure 1: **Simplified cross section of a solid tumour**

Who does cancer affect and what does it cost?

Cancer can affect anyone, and there can be few families that do not have a relative or friend who has some form of cancer. It affects one in three people at some time in their lives, though some tumours are much less common than others. In the UK, the commonest form in women is breast cancer, followed by colorectal (bowel), lung, ovarian and uterine cancer. In men, prostate cancer is the most common, followed by lung, colorectal and bladder cancer.

The NHS is estimated to have spent £3.4 billion treating cancer in 2003-04. To this figure must be added the costs for community health services, non-professional (family) carers and lost productivity.

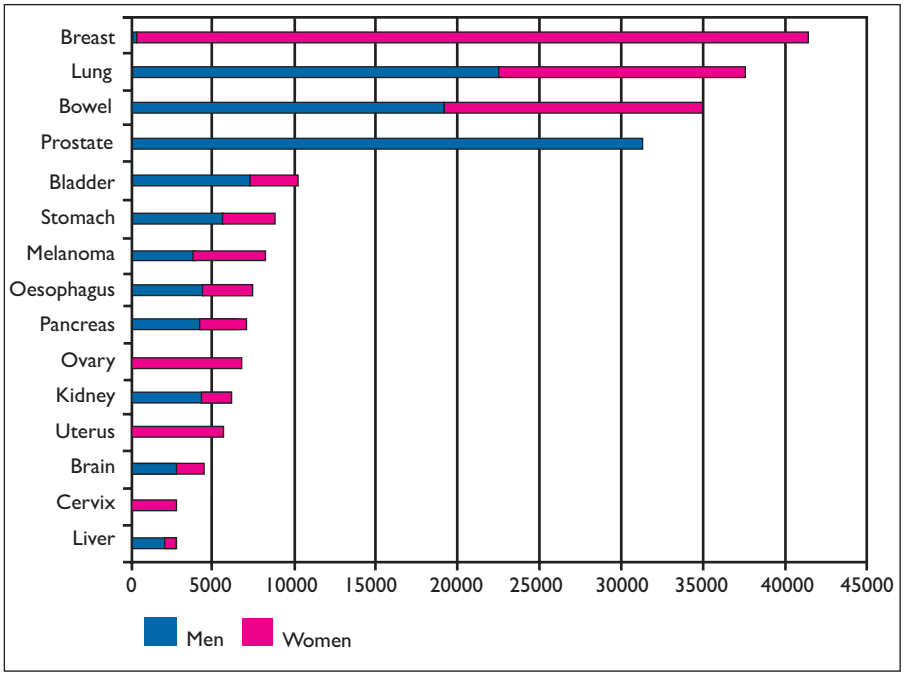

Figure 2: **Numbers of new cases of the most common cancers in the UK in 2002. Excluding blood cancers and non-melanoma skin cancer.**
(Based on data from Cancer Research UK.)

Present treatments and shortcomings

It is not possible to detail here all the available treatments for cancer and their side effects, many of which are well known. Radiotherapy, surgery and chemotherapy are all used for treatment, depending on the tumour type. There are several classes of chemotherapy agents and it is common for cancer specialists to use combinations of several medicines, to maximise their effectiveness. Some can make the recipient feel very unwell, causing nausea and loss of hair, and depress the immune system, leaving the patient vulnerable to infection. Other side-effects include loss of fertility, as well as liver or cardiac damage. Supportive medications, such as anti-emetics, may be given to minimise adverse effects. Medicines used for hormone-dependent tumours (e.g. breast and prostate cancer) are generally better tolerated than the older alkylating agents.

Table 1: **Selected anti-cancer medicines used to treat solid tumours**

CLASS	EXAMPLES	USES*
Alkylating agents	Carboplatin (Paraplatin, Bristol-Myers Squibb) Carmustine (Bicnu, Bristol-Myers Squibb) Chlorambucil (Leukeran, GlaxoSmithKline) Cisplatin (Platinex, Bristol-Myers Squibb) Cyclophosphamide (Pfizer) Melphalan (Alkeran, GlaxoSmithKline) Temozolamide (Temodal, Schering-Plough)	Ovarian, small-cell lung cancer Brain tumours Breast, ovarian cancer Testicular, cervical, bladder, ovarian, lung cancer Various cancers, esp. breast, lung Breast, ovarian cancer Malignant glioma
Anti-metabolites	Capecitabine (Xeloda, Roche) Gemcitabine (Gemzar, Lilly) Tegafur-uracil (Uftoral, Merck Pharmaceuticals) 5-fluorouracil (Medac) Methotrexate (Maxtrex, Pfizer) Raltitrexed (Tomudex, AstraZeneca)	Colorectal, breast cancer Bladder, pancreatic, non small-cell lung cancer Colorectal cancer Breast, colorectal cancer Breast, lung, ovarian, head & neck, bladder cancer, etc Colorectal cancer
Topoisomerase inhibitors	Etoposide (Vepesid, Bristol-Myers Squibb) Irinotecan (Campto, Pfizer) Topotecan (Hycamtin, Merck Pharmaceuticals)	Testicular, small-cell lung cancer Colorectal cancer Ovarian cancer, small-cell lung cancer, cervical cancer
Cytotoxic antibiotics	Dactinomycin (Cosmegen Lyovac, MSD) Epirubicin (Pharmorubicin, Pfizer) Idarubicin (Zavedos, Pfizer)	Testicular, uterine cancer, rhabdomyosarcoma Breast, ovary, stomach, lung, colon, bladder cancer Breast cancer
Microtubule disruptors	Docetaxel (Taxotere, sanofi aventis) Paclitaxel (Taxol, Bristol-Myers Squibb) Vincristine (Oncovin, Lilly) Vinorelbine (Navelbine, Pierre Fabre)	Breast, non small-cell lung cancer Breast, ovarian, non small-cell lung cancer Breast, small-cell lung, head & neck cancers Breast, non small-cell lung cancer
Hormonal agents	Bicalutamide (Casodex, AstraZeneca) Flutamide (Drogenil, Schering-Plough) Cyproterone acetate (Cyprostat, Schering) Triptorelin (Decapeptyl SR, Ipsen) Goserelin (Zoladex, AstraZeneca) Fulvestrant (Faslodex, AstraZeneca) Leuprorelin (Prostap, Wyeth) Tamoxifen (Nolvadex, AstraZeneca) Toremifene (Fareston, Orion)	Prostate cancer Prostate cancer Prostate cancer Prostate cancer Breast, prostate cancer Breast cancer Prostate cancer Breast cancer Breast cancer
Aromatase inhibitors	Anastrozole (Arimidex, AstraZeneca) Exemestane (Aromasin, Pfizer) Letrozole (Femara, Novartis)	Breast cancer Breast cancer Breast cancer
Monoclonal antibodies	Trastuzumab (Herceptin, Roche) Bevacizumab (Avastin, Roche) Cetuximab (Erbitux, Merck Pharmaceuticals)	Breast cancer Colorectal cancer Colorectal, head & neck cancer
Other agents	Interferon alpha-2b (Intron A, Schering-Plough) Imatinib (Glivec, Novartis) Sunitinib (Sutent, Pfizer)	Kaposi's sarcoma, melanoma Gastrointestinal stromal tumours Kidney cancer, gastrointestinal stromal tumours

* Not all uses are listed here

Radiotherapy may be helpful in reducing the size of a tumour before surgical removal or to eliminate any cells remaining after surgery. Chemotherapy used for this purpose is known as *adjuvant therapy*. The disadvantages of radiotherapy mainly arise from the unavoidable irradiation of surrounding healthy tissue or organs - the intestines and kidneys are particularly sensitive. The shortcomings of chemotherapeutics, apart from their toxicity, relate mainly to lack of efficacy. Many tumours are initially very responsive to chemotherapy, but the impact on survival still remains small in many cases and complete cures are difficult to achieve. Hence there is a great need for more effective and less toxic forms of medication for most solid tumours.

What's in the development pipeline?

The development of new anti-cancer medications is made especially difficult by the fact that cancerous cells differ very little

Table 2: **Selected company clinical trial activity against solid tumours**

Company	*Breast*	*Colon*	*Lung*	*Ovary*	*Pancreas*	*Prostate*	*Melanoma*	*Kidney*	*Other Tumours*	*Supportive Therapy*
Abbott						●			●	
Amgen	●	●	●						●	●
Antisoma	●		●	●		●		●	●	
Astellas			●			●	●			
AstraZeneca	●		●			●			●	
Bayer			●				●	●	●	
Biogen Idec			●	●	●		●	●	●	
Bristol-Myers Squibb	●						●		●	
Eisai	●	●	●			●			●	
Genzyme			●			●	●		●	●
GlaxoSmithKline	●		●	●		●	●	●	●	●
Introgen	●		●						●	
Ipsen	●					●			●	
Ligand	●		●					●		
Lilly	●	●	●	●	●	●			●	
Menarini		●		●					●	
Merck Pharmaceuticals	●	●	●	●	●		●		●	
Merck Sharp & Dohme						●			●	●
Novartis		●	●				●	●	●	
OSI			●	●					●	●
Oxford BioMedica		●			●			●		
Pierre Fabre	●		●			●			●	
Pfizer	●	●	●		●	●	●	●	●	
PharmaMar	●	●	●	●		●	●		●	
Roche	●	●	●	●	●	●		●	●	●
Sanofi-aventis	●				●	●			●	●
Schering	●	●	●	●		●			●	
Schering-Plough	●						●			
Wyeth	●		●					●	●	

from the non-cancerous cells from which they arise. Designing medicines that act selectively on tumour cells and not, or as little as possible, on healthy cells depends on developing a deep knowledge of the causes of malignant transformation, and of the biological changes that distinguish a cancerous cell from a normal one. Knowledge of the molecular, genetic and biological characteristics of tumour cells has improved greatly in recent decades and newer anti-cancer medicines are generally much more specific in the way they work than older cytotoxic (cell-killing) medicines.

Many clinical development projects are underway to develop new treatments for cancers, and it is not possible to do more than summarise a few of the new projects that concern the major types of cancers. Table 2 gives an overview of where companies have investigations in progress.

BREAST CANCER is often treatable with surgery, followed by radiotherapy or chemotherapy. For the majority whose breast tumours are dependent on steroids for growth, steroid receptor blockers such as tamoxifen can prevent recurrence and the development of metastases. Other compounds of this type include toremifene (Fareston, Orion) and, for advanced breast cancer, fulvestrant (Faslodex, AstraZeneca) and the aromatase inhibitors anastrozole (Arimidex, AstraZeneca), exemestane (Aromasin, Pfizer) and letrozole (Femara, Novartis). In advanced metastatic breast cancer where cytotoxic therapy has failed, the microtubule inhibitors paclitaxel (Taxol, BMS), docetaxel (Taxotere, sanofi-aventis) or vinorelbine (Navelbine, Pierre Fabre) may be considered. The monoclonal antibody trastuzumab (Herceptin, Roche) has also been shown to improve survival in advanced breast cancer where the tumour is herceptin receptor (HER2)-positive.

NEW SINCE 2000

2000 - Anastrozole (Arimidex, AstraZeneca) first line use in advanced Breast Cancer

2000 - Exemestane (Aromasin, Pfizer) adjuvant use in early BC

2000 - Trastuzumab (Herceptin, Roche) metastatic BC

2002 - Capecitabine (Xeloda, Roche) metastatic BC

2004 - Fulvestrant (Faslodex, AstraZeneca) advanced BC

2004 - Gemcitabine (Gemzar, Lilly) metastatic BC

2005 - Anastrozole (Arimidex, AstraZeneca) early BC

2005 - Letrozole (Femara, Novartis) early BC

2006 - Trastuzumab (Herceptin, Roche) early BC

New compounds which work in a wide range of ways are in clinical development. Three new **microtubule-disrupting agents** are in Phase 3 trial: Eisai's E-7389, sanofi-aventis's XRP 9881 (larotaxel), and Bristol-Myers Squibb's ixabepilone, an agent of a new type that binds to microtubules in a different way from taxanes. Schering also has a compound of this type (ZK-EPO) in Phase 2 trial, Bristol-Myers Squibb also has a new taxane (BMS-184476) at Phase 2, and sanofi-aventis's new taxoid (XRP 6258) has reached this stage as well.

New **monoclonal antibodies** are also in development for treating breast cancer:

- Bevacizumab (Avastin, Roche), which binds to vascular endothelial growth factor (VEGF) and prevents it from stimulating the growth of new blood vessels into tumours, is authorised for use in colorectal cancer and is now in Phase 3 trial in metastatic breast cancer
- Cetuximab (Erbitux, Merck Pharmaceuticals), also available for use in colorectal cancer, is now in Phase 2 trial for breast cancer treatment. It binds to epidermal growth factor (EGF) receptors on tumour cells, inhibiting cell growth and repair, and is given together with chemotherapy

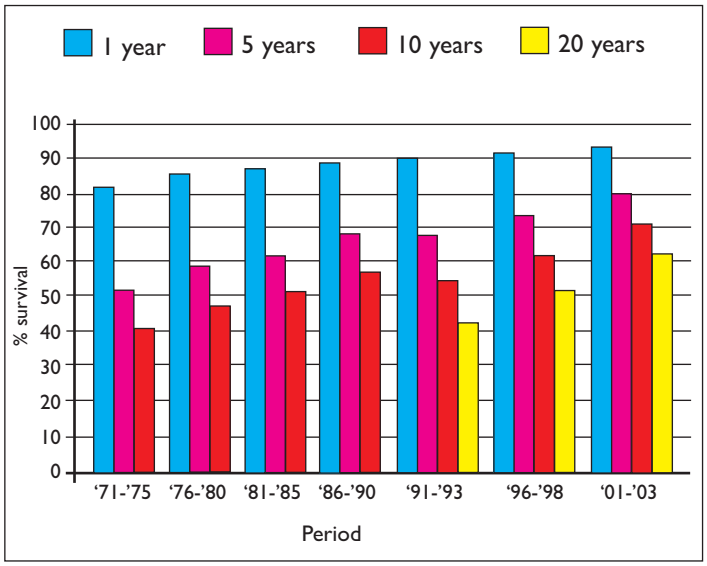

Figure 3: **Survival at one, five, ten and twenty years for patients with female breast cancer in England and Wales, 1971-2003**

- Adecatumumab (MT201), which binds to a tumour cell surface protein known as epithelial cell adhesion molecule (Ep-CAM), enabling antibodies and the complement system in blood to kill the tumour cells selectively, is being developed in Phase 2 studies by Serono
- Antisoma's AS1402, which binds to the MUC-1 cell membrane protein of tumours of epithelial cell origin, helping the body to kill them selectively, has progressed to Phase 2 trial in metastatic breast cancer
- Amgen's denosumab, which binds to a key protein (RANK ligand) of bone cells, has been shown in Phase 2 trials to suppress the bone turnover (leading to pain and fractures) associated with metastases in patients with advanced breast cancer and is now in Phase 3 trial
- Imclone Systems has IMC-18F1, binding to the type 1 receptor for VEGF, in Phase 1 trial.

Tyrosine kinase inhibitors make up another class of new medicines for treating breast cancer. Lapatinib (Tykerb, GlaxoSmithKline) inhibits the tyrosine kinase associated with cell proliferation, tissue invasion and metastasis in various cancers. In a Phase 3 trial in advanced or metastatic breast cancer, lapatinib, given together with capecitabine, significantly increased the time to tumour progression. Lapatinib is being studied further for its potential in treating metastases that have spread to the brain.

Other late-stage projects involve new oral therapies or developments of agents already authorised for use in other cancers. In Phase 3 trial are the aromatase inhibitor exemestane (Aromasin, Pfizer) for prevention rather than treatment, capecitabine (Xeloda, Roche) for use in combination with other agents, and the compound temsirolimus (Wyeth), which arrests cell growth and is in development for advanced breast cancer. Pfizer has sunitinib malate, which inhibits the growth of a new blood supply into tumours, in Phase 3 study and a similar compound (SU-14813) at Phase 2. Other compounds at Phase 2 include ispinesib (Cytokinetics) that stops cells proliferating and lonafarnib (Sarasar, Schering-Plough), another cell growth inhibitor.

NEW SINCE 2000

2001 - Capecitabine (Xeloda, Roche) metastatic CRC

2001 - Tegafur-uracil (Uftoral, Merck Pharmaceuticals)

2004 - Cetuximab (Erbitux, Merck Pharmaceuticals) metastatic CRC

2004 - Oxaliplatin (Eloxatin, sanofi-aventis)

2004 - Irinotecan (Campto, Pfizer) advanced CRC

2005 - Bevacizumab (Avastin, Roche) metastatic CRC

COLORECTAL CANCER (CRC) is a major cancer type in which chemotherapy may have only moderate success, partly because the disease is often not detected until an advanced stage. Chemotherapy is often used after surgery (*adjuvant chemotherapy*) or to shrink the tumour in advanced disease. The medicines most often used for this purpose are 5-fluorouracil (5-FU), which is often given together with folinic acid (Isovorin, Wyeth), irinotecan (Campto, Pfizer), and oxaliplatin (Eloxatin, sanofi-aventis). The combination of 5-FU, folinic acid and oxaliplatin is often known as the FOLFOX regimen. Capecitabine (Xeloda, Roche) and tegafur-uracil (Uftoral, Merck Pharmaceuticals) are compounds that are broken down to 5-FU at the tumour site and are taken orally, whereas 5-FU itself is given by injection. More recently, two monoclonal antibodies have been made available for use in metastatic colorectal cancer (CRC). These are bevacizumab (Avastin, Roche) and cetuximab (Erbitux, Merck Pharmaceuticals).

As in breast cancer, new **monoclonal antibodies** are among the agents being developed as new therapies for colorectal cancer. Panitumumab (Amgen) has been shown to reduce the rate of tumour progression in people with metastatic CRC who had failed to respond to chemotherapy. (Panitumumab is also in clinical trials against lung and head and neck cancer.) Matuzumab (Merck Pharmaceuticals) is a monoclonal antibody against Epidermal Growth Factor Receptor (EGFR - a receptor on cells that responds to a factor that promotes the growth and division of cells) that is currently in Phase 2 trial in CRC. Mapatuzumab (Human Genome Sciences) is a monoclonal antibody that acts by making tumour cells self-destruct through a natural process known as programmed cell death (called *apoptosis*). This antibody is also in Phase 2 trials. In addition, Roche is conducting a Phase 3 study of bevacizumab (Avastin) to see whether, in combination with the FOLFOX regimen, or in combination with oxaliplatin + capecitabine, it can reduce the risk of the cancer recurring in people with no evidence of disease after curative surgery for CRC. Merck Pharmaceuticals is also continuing to explore cetuximab (Erbitux) combinations with irinotecan and oxaliplatin in additional Phase 3 trials at earlier stages of CRC.

Several small molecule compounds have reached Phase 2 testing, including pemetrexed from Eli Lilly, Cytokinetics' ispinesib, and sunitinib malate (Sutent, Pfizer).

Oxford Biomedica has reported promising Phase 2 results in trials in metastatic CRC with a therapeutic vaccine (TroVax) that introduces a gene into tumour cells to stimulate an immune response. Survival results were sufficiently encouraging for this vaccine to be taken into Phase 3 study in early stage CRC.

Survival rates in CRC have been improving steadily over the last 30 years and the average 5-year survival rate now exceeds 50 per cent. Many factors have contributed to this, but it is encouraging to see that chemotherapy results have also improved over this period. With the planned introduction of a national screening programme for CRC, and the identification of new tests for detecting the disease, more cases may be detected in the early stages of disease, where the outcome of treatment is better. If this can be achieved, then the prospect is for continuing improvement in coming years.

LUNG CANCER is a form of cancer which can be very difficult to treat, with average survival time from diagnosis of approximately six months to one year. Platinum compounds (carboplatin, cisplatin), anti-metabolites (gemcitabine, methotrexate), microtubule inhibitors (vincristine, vinorelbine, paclitaxel, docetaxel) and the topoisomerase inhibitor etoposide are often used for chemotherapy, usually in combination, but side-effects can limit therapy.

One promising new class of medicines that may help to extend survival is the **kinase inhibitors**. These inhibit enzymes closely involved in key cell functions and their effects vary according to which enzymes they inhibit. Many, but not all, of them are given orally. Erlotinib (Tarceva, Roche) has already shown a survival benefit in advanced non-small cell lung cancer (NSCLC) and is indicated for use in advanced disease where chemotherapy has failed. It is now in Phase 3 trial to see whether it is also effective in those who have not already undergone chemotherapy. AZD2171 (AstraZeneca), which works in a similar way, is in Phase 2/3 trial. AstraZeneca also has ZD6474 in Phase 3 trial for NSCLC. Another multi-kinase inhibitor that targets an even wider range of enzymes is sorafenib, from Bayer and Onyx, which has now entered Phase 3 study. Other kinase inhibitors in Phase 2 development include Cyclacel's seliciclib, XL999 (Exelixis), sunitinib malate (Sutent, Pfizer) and Wyeth's HKI-272.

Several **monoclonal antibodies** are being investigated in NSCLC. Cetuximab (Erbitux, Merck Pharmaceuticals) and bevacizumab (Avastin, Roche) are in Phase 3 trial, while mapatumumab (Human

NEW SINCE 2000

2005 - Vinorelbine, oral (Navelbine, Pierre Fabre)

2005 - Erlotinib (Tarceva, Roche) advanced NSCLC

2006 - Topotecan (Hycamtin, sanofi-aventis) relapsed SCLC

Genome Sciences) and matuzumab (Merck Pharmaceuticals) are at Phase 2. Others in development include CDP-791 (UCB, Phase 2), nimotuzumab (YM Biosciences, Phase 2) and panitumumab (Amgen, Phase 1).

A variety of **cell cycle-disrupting** agents are in Phase 2 development, including E7389 and E7070 (Eisai), Tasidotin (Genzyme) and ispinesib (Cytokinetics).

Vaccine approaches are also being tried. Aphton Biopharma's IGN101 stimulates an immune response against a protein on some tumour cells (EpCAM) and is in Phase 2/3 trial. Merck Pharmaceuticals is developing a vaccine (L-BLP25, Stimuvax), which has entered Phase 3 trial. In a Phase 2 trial, patients with stage IIIB NSCLC given the vaccine showed an average survival time of 30.6 months, compared with 13.3 months in those not given the vaccine. GlaxoSmithKline also has a therapeutic vaccine which is in Phase 2 study.

Among other advanced projects are pemetrexed (Alimta, Eli Lilly; Phase 3), Pfizer's PF-3512676 (Phase 3), Telik's TLK-286 (Phase 3), Antisoma's AS1404 (Phase 3), Introgen's Advexin (Phase 2), Millennium's bortezomib (Phase 2), Schering's MS-275 and ZK-EPO (both Phase 2) and Sunesis Pharma's SNS-595 (Phase 2).

With such a large array of new initiatives under development, it must be hoped that survival rates in non-small cell lung cancer, which have hardly risen over the last twenty years, can be substantially improved.

OVARIAN CANCER is less common than lung cancer, but is still a significant cause of death. New therapies are needed, as five year survival rates are still below 30 per cent and relatively few medicines are authorised for use in ovarian cancer. GlaxoSmithKline's topotecan (Hycamtin) is in Phase 3 trial for first-line use, as is Roche's bevacizumab (Avastin) and the microtubule stabiliser patupilone (EPO 906) of Novartis. A completely new agent also at Phase 3 is PharmaMar's trabectedin, a molecule originally discovered in a marine organism, that inhibits cell division and DNA repair.

Compounds in Phase 2 trials include Eli Lilly's pemetrexed, Antisoma's AS1404, ispinesib (Cytokinetics), Schering's ZK-EPO and Roche's pertuzumab (Omnitarg). OSI Pharmaceuticals is testing a form (OSI-211) of lurtotecan in Phase 2 for relapsed ovarian cancer. Menarini's abagovomab is being prepared for Phase 3 studies in prevention/delay of relapse.

PANCREATIC CANCER is another condition with very poor treatability. 5-FU and gemcitabine (Gemzar, Lilly) are the main chemotherapy medicines used, often together with radiotherapy, but response rates are not encouraging and survival is usually only a matter of months. The first agent to have shown a significant increase in survival when added to standard gemcitabine chemotherapy is erlotinib (Tarceva, Roche). However, the survival rate was still low, with only 24 per cent of patients alive after one year.

Phase 3 trials in progress include studies of the monoclonal antibodies cetuximab (Erbitux, Merck Pharmaceuticals) and bevacizumab (Avastin, Roche) and of the cytotoxic agents (those that kill the cancer cells) capecitabine (Xeloda, Roche), tegafur-uracil (Uftoral, Merck Pharmaceuticals) and a new microtubule inhibitor XRP 9881 (Larotaxel, sanofi-aventis). Among new cytotoxic agents at Phase 2 is Eisai's cell cycle disrupting agent E7070 (indisulam) and Pfizer's multi-targeted kinase inhibitor AG 13736 (axitinib).

Also at Phase 2, GenVec is exploring a gene therapy approach. Direct injection of this material (TNFerade) into the tumour, followed by chemotherapy, causes the generation of an anti-cancer substance called tumour necrosis factor-alpha (TNFα) in the tumour itself. Oxford BioMedica is also using a gene therapy approach with their agent MetXia, which delivers a gene into the tumour, where it stimulates local production of a cytotoxic substance. It is hoped that this strategy will result in enhanced elimination of tumour cells.

PROSTATE CANCER has a much better prognosis than pancreatic cancer. While a tumour confined within the prostate itself is usually treated by surgery (radical prostatectomy) or radiation therapy, about half of all cases have already metastasised by the time they are discovered and require additional treatment. This usually involves therapy with hormonal agents such as gonadotrophin releasing hormone (GnRH) agonists triptorelin (Decapeptyl, Ipsen), leuprorelin (Prostap, Wyeth), buserelin (Suprefact, sanofi-aventis) or goserelin (Zoladex, AstraZeneca) or anti-androgens, e.g. flutamide, bicalutamide or cyproterone acetate. Typically, these are prescribed for advanced disease. However, bicalutamide (Casodex, AstraZeneca) is also used in non-metastatic disease. Docetaxel (Taxotere, sanofi-aventis) is also available for treatment of metastatic disease that has not responded to hormonal treatment.

Medicines development has tended to concentrate on agents for treating late-stage disease. A number of new small molecule agents are in Phase 2 development, including:

- Ambrilia Biopharma's Laminin receptor binding peptide PCK3145
- Antisoma's vascular targeting agent DMXAA (AS1404)
- Astellas's survivin expression inhibitor YM-155
- AstraZeneca's endothelin-A receptor antagonist ZD 4054
- Genzyme's tubulin-disrupting dolastatin analogue Tasidotin
- OncoGenex's clusterin-inhibiting antisense oligonucleotide OGX-011
- Pfizer's multi-targeted kinase inhibitor sunitinib malate (Sutent)
- PharmaMar's marine-derived cyclic peptide Aplidin
- YM BioScience's chemopotentiator tesmilifene.

These compounds are generally at too early a stage of development for their efficacy to be judged. However, some encouraging data on efficacy are available for a number of **anti-tumour vaccines** that have progressed further in development. Cell Genesys has a vaccine (GVAX) comprised of two genetically modified prostate cancer cell lines. It is in Phase 3 trials in patients with metastatic disease. Dendreon Corp is also developing a prostate cancer vaccine (sipuleucel-T, PROVENGE) and has reported results from a Phase 3 trial in patients with hormone-resistant metastatic cancer. In this study, 34 per cent of those who had received the vaccine were alive at 36 months as compared with 11 per cent who had been given placebo. Onyvax has started a Phase 3 trial of its Onyvax-P vaccine, which contains antigens from three prostate cancer cell lines. In addition, Oxford bioMedica is studying its TroVax vaccine in prostate cancer

(Phase 2). Results from these various projects so far suggest that vaccines may represent a promising new approach to the treatment of advanced prostate cancer.

Monoclonal antibodies are also being explored in prostate cancer. Bevacizumab (Avastin, Roche) has reached Phase 3 trial, as has denosumab (Amgen), which is being studied for its effects on bone metastases. Monoclonal antibodies in Phase 2 study include MDX-070 (Medarex), adecatumumab (MT201, Serono), and MLN2704. In addition, Merck Sharp & Dohme is developing AGS-PSCA in Phase 1 trial and Pfizer is developing CP-751871, a monoclonal antibody to IGF-1R, at the same stage.

While some prostate tumours progress only slowly, others are much more invasive, giving rise to bone metastases and markedly reducing survival. Unfortunately, tests are not yet available to determine the risk of progression. The commonly-measured prostate specific antigen (PSA) has been found to be an unreliable marker of the progression of malignancy. Several genes have now been suggested to be better markers, including the E2F3 gene identified by researchers at the Institute of Cancer Research of the University of London, and development of a reliable diagnostic test would be a great advance in managing this common cancer.

OTHER TUMOUR TYPES are less common, but the need to improve chemotherapy is just as acute and pharmaceutical companies have included them in their development programmes. There are development projects in many more areas than just the six detailed above.

- Recent positive developments in **kidney cancer** include the introduction of sorafenib (Nexavar, Bayer) and sunitinib (Sutent, Pfizer), while Wyeth's temsirolimus, GlaxoSmithKline's lapatinib and pazopanib, Novartis's rapamycin derivative RAD 001 (everolimus) and Roche's bevacizumab are all in Phase 3 trial.
- In **brain cancer**, temozolomide (Temodal, Schering-Plough), for newly-diagnosed glioblastoma, and carmustine implants (Gliadel implants, Link Pharmaceuticals) for malignant glioma have increased the therapeutic options available, while Eli Lilly's enzastaurin and Novartis's imatinib (Glivec) are in Phase 3 trials for glioblastoma.
- The arrival of cetuximab (Erbitux, Merck Pharmaceuticals) for locally advanced squamous cell carcinoma of the **head and neck** is a welcome advance and Amgen is studying panitumumab for this use (Phase 3).

Supportive treatment

Improved supportive treatments are also needed for chemotherapy to be applied productively and a range is in development that address the major side effects that can limit therapy.

- **Anaemia** may develop during chemotherapy and can now be managed using darbepoetin alpha (Aranesp, Amgen) and epoetin beta (Neorecormon, Roche). Roche also has a new preparation (R774, CERA) in Phase 2 trial.
- **Mucositis of the mouth and throat** is often seen with radiotherapy and high-dose chemotherapy and palifermin (Kepivance, Amgen) is available for treating this. Other compounds in development for this use include RK-0202 (RxKinetix) and ATL-104 (Alizyme), which have both completed Phase 2 studies.
- **Nausea and vomiting** is also a problem with chemotherapy, especially where it involves platinum compounds. Several effective compounds that much reduce this problem are now available, and Merck Sharp & Dohme has aprepitant (Emend), a new class of anti-emetic. GlaxoSmithKline has a further compound of this type in development: casopitant (Phase 3).

A great deal of effort is being put into researching anti-cancer medicines and there has been real progress over the past decade. Nevertheless, achieving long-term disease-free survival in many solid tumours remains an ambitious goal rather than an accomplished fact. Over time, however, as increasingly selective agents are developed, backed up by growing insight into the biology of cancer, disease management is being improved and patients' quality of life and life expectancy are being continually improved.

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OR

Prostate Cancer Support Association, BM Box 9434, London WC1N 3XX
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OR

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CARDIAC ARRHYTHMIA

What are cardiac arrhythmias?

Arrhythmias are disturbances to the natural rhythm of the heart. The heart has a 'pacemaker', called the sinus node, in the atrium of the right hand side of the heart. This generates electrical impulses that are transmitted through specialised conductive tissues to the muscles of the right and left ventricles, where they cause the muscular contractions that pump blood around the body (Figure 1). The normal beating of the heart is considered to range between 60 and 100 beats per minute under resting conditions. Arrhythmias take the form of a speeding up (*tachycardia*) or slowing down (*bradycardia*) of the rate outside these limits, or of the insertion or deletion of beats from the normal pattern. An arrhythmia may be *supraventricular* - caused by a process occurring in the atrium, situated above the ventricle - or *ventricular*.

Some cardiac arrhythmias are medically of little significance. For example, many people will have experienced occasional extra beats or palpitations, but these do not usually require therapy, while others may be rapidly fatal (e.g. ventricular fibrillation) if not treated at once. Some are of clinical significance, but are treated by surgery or the implantation of an artificial pacemaker (e.g. supra-ventricular tachycardia). Atrial fibrillation is the most common type of medically treated chronic arrhythmia. In itself it is not a major cause of death, but it is linked to an increased risk of heart failure and stroke. It is associated with coronary heart disease, high blood pressure, rheumatic heart disease or hyperthyroidism, and requires treatment alongside these conditions.

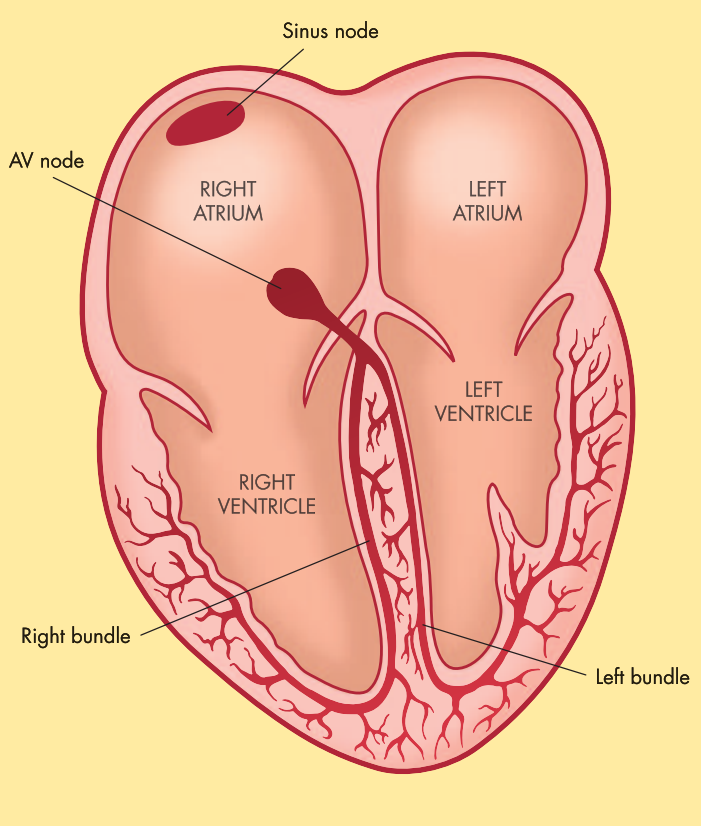

Figure 1: **The conductive tissue of the heart**

Who do arrhythmias affect?

In the 2003 Health Survey for England, 2.8 per cent of adult respondents reported that they had experienced abnormal heart rhythm during the previous 12 months and about 5.3 per cent had experienced it at some stage in their lives. The prevalence of arrhythmia increases significantly with age in both men and women (Figure 2).

Cardiac arrhythmias were the main cause of death in just over 3,000 deaths in England and Wales in 2004, of which 2,836 deaths were attributed to atrial fibrillation. However, AF is a contributory cause of death in many more cases, where the main cause may be recorded as heart attack, stroke or heart failure.

The direct cost to the NHS of treating atrial fibrillation has been estimated to be £459 million in 2000, with a further £111 million being spent on nursing home care.

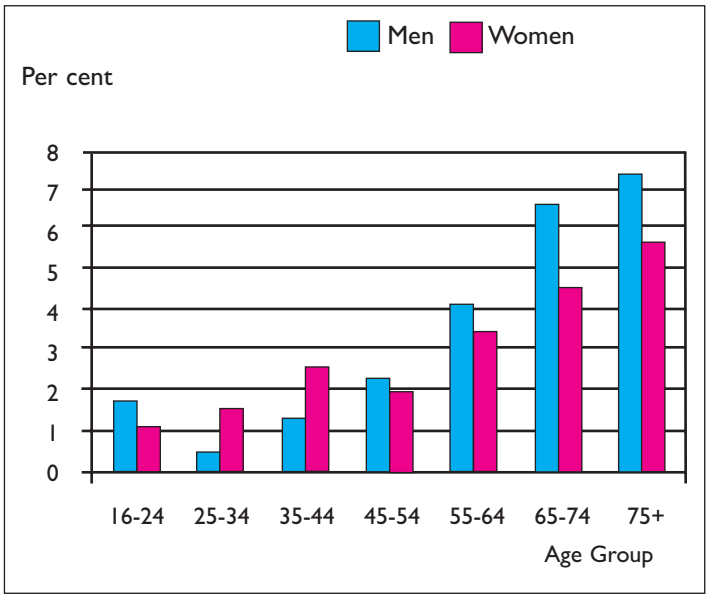

Figure 2: **Prevalence of abnormal heart rhythm in the past 12 months**
Source: Health Survey for England, 2004

Present treatments and shortcomings

Atrial fibrillation (AF) may occur as recurrent episodes that resolve spontaneously *(paroxysmal)*, as episodes that persist for more than 7 days and do not clear up *(persistent)*, or as an established pattern *(permanent)*. In paroxysmal AF, an attempt will usually be made to re-establish normal rhythm, either by electric shock or by treatment with medication. Once normal rhythm is re-established, other medication may be required to maintain an AF-free state. Where AF has become established, or initial treatment has been unsuccessful, medication may instead be given to slow down

excessively rapid heartbeat. Because AF is associated with a much increased risk of stroke and thrombosis, many people are also given anticoagulant treatment (one which prevents clotting) with either aspirin or, in higher risk cases, with warfarin.

Medications used to treat arrhythmias have been grouped into four main classes. Those in class 1 (subdivided into three sub-classes, according to their effects) are sodium channel blockers, class 2 are the beta-blockers, class 3 medicines are potassium channel blockers and class 4 anti-arrhythmic medicines are calcium channel blockers. Beta-blockers and calcium antagonists, along with digoxin, are commonly used to slow rapid heartbeat (rate control), whereas beta-blockers, class 1c agents (e.g. flecainide) and class 3 drugs are mainly used for rhythm control.

Many of the existing anti-arrhythmic treatments are not well tolerated. Gastrointestinal side effects (nausea, vomiting, diarrhoea, pain, etc) are common with class 1 medicines such as quinidine (Kinidin Durules, AstraZeneca) and mexiletine (Mexitil, Boehringer Ingelheim), visual disturbances and urinary retention may occur with disopyramide (Rythmodan, sanofi-aventis) and blood disorders and moderate to severe skin rashes can develop with phenytoin (Epanutin, Pfizer). Beta-blockers are generally well tolerated, except for causing lethargy, but the potassium channel blocking class 3 anti-arrhythmic medicines, particularly amiodarone (Cordarone X, sanofi-aventis), must be used with caution, as they may actually cause arrhythmia in certain situations and a potentially life-threatening abnormal heart rhythm has been observed with several class 3 medicines.

What's in the development pipeline?

Several new anti-arrhythmic compounds have reached the Phase 3 stage.

- Jointly developed by Cardiome and Astellas, RSD 1235 is a new agent that acts on both sodium and potassium ion channels in the heart. An intravenous form is completing Phase 3 studies for use in terminating AF and restoring heart rhythm. An oral, controlled-release form is also in development for the prevention of recurrence of AF, and this has reached Phase 2.
- Sanofi-aventis's dronedarone (Multaq) is chemically related to the widely-used agent amiodarone and has been developed to offer better safety and tolerability. It has shown efficacy in Phase 3 trials in preventing recurrence of atrial fibrillation and in re-establishing a normal heartbeat. A back-up compound (SSR 149744) has reached Phase 2 study.
- Solvay's tedisamil (Pulzium), a new class 3 potassium channel blocker, has completed Phase 3 clinical development in recent-onset AF.
- Procter & Gamble's azimilide (Stedicor), a new class 3 anti-arrhythmic, is in Phase 3 trial for supraventricular tachycardia, a serious arrhythmia that is otherwise mainly treated by surgery.

Blocking the angiotensin-II type 1 receptor has been observed to reduce the incidence of episodes of AF in patients with paroxysmal AF and several of the medications of the ARB class already available for use to treat hypertension are now being explored for their possible use in AF. Olmesartan (Olmetec, Daiichi-Sankyo) is in Phase 3 trial in paroxysmal AF, irbesartan (Aprovel, Bristol-Myers Squibb/sanofi-aventis) is being studied for AF prevention and prevention of cardiac remodelling in those at risk of AF, and valsartan (Diovan, Novartis) is in Phase 4 trial for reduction of recurrence in patients who have been treated for persistent atrial fibrillation.

At the Phase 2 stage, Aryx Therapeutics is developing a new analogue of amiodarone (ATI-2042), sanofi-aventis has celivarone (SSR 149744) and Solvay has odiparcil, which is in development as an alternative to warfarin for the prevention of stroke in AF. Also new at Phase 2 is Wyeth's rotigaptide, which works by a process known as gap junction modulation and is the first potential anti-arrhythmic to use this approach.

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CONGESTIVE HEART FAILURE

What is congestive heart failure?

Congestive heart failure (CHF) is defined as the inability of the heart to pump a sufficient volume of blood to meet the body's requirements. Breathlessness and fatigue are its most common symptoms, along with swelling of the ankles and legs, as a result of retained fluid. The most common form of heart failure is that in which the muscle of the left ventricle (lower chamber) of the heart weakens, leading to a reduced pumping ability (known *as left ventricular systolic dysfunction*), but elderly people may develop heart failure while retaining normal systolic function. Heart failure is often a consequence of some other disease which has damaged the heart, such as coronary artery disease, hypertension, prior heart attack, heart valve or muscle disease, diabetes, or severe lung disease. Fluid retention may lead to complications such as kidney damage.

As the heart weakens, the body initially tries to compensate for its reduced output by producing a variety of so-called neurohormones, including noradrenaline, angiotensin 2, aldosterone, endothelins, antidiuretic hormone (vasopressin), natriuretic peptides, and cytokines, including pro-inflammatory cytokines such as IL-1, IL-6 and Tumour Necrosis Factor-alpha (TNF-α). In the longer term, this reaction further damages the heart, leading to progressive changes in heart structure and function, known as remodelling, that are ultimately fatal. Newer medical therapies for heart failure attempt to interrupt this neurohormonal response, stop disease progression and lower death rates, as well as providing the symptomatic relief important for quality of life.

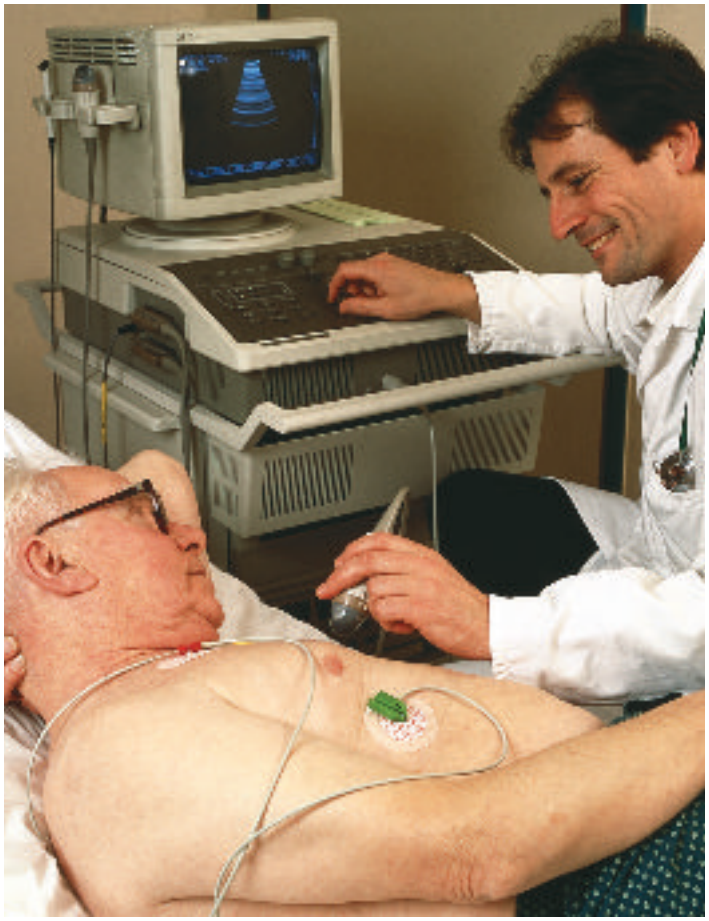

Figure 1: **Echocardiography may be used to detect changes in heart size and function in CHF.**

Who does congestive heart failure affect and what does it cost?

A study found that approximately 3 per cent of adults aged 45 or over had definite or probable heart failure. The incidence of heart failure rises steeply with age and men are more likely to be affected than women, especially below the age of 65. Between 50-60 per cent of people admitted to hospital with CHF die within five years. Heart failure of all types was responsible for over 106,000 cases of hospital-based treatment and 9,156 deaths in England and Wales in 2004/5. However, these statistics are likely to be underestimates of the true figures. It has been estimated that over 980,000 people require treatment for heart failure in the UK and that the direct cost to the NHS in 2000 would have been £905 million (with hospitalisation accounting for about 70 per cent of this).

Present treatments and shortcomings

NICE guidelines for the treatment of CHF recommend initial use of an ACE inhibitor, or, if an ACE inhibitor is not tolerated, candesartan (Amias, Takeda) or valsartan (Diovan, Novartis), together with a diuretic, to control water retention and adverse neurohormonal response (see above). Later, a beta-blocker may be added - typically bisoprolol (Cardicor, Merck Sharp & Dohme) or carvedilol (Eucardic, Roche), as these have been shown to be effective in lowering death rates in CHF. If this combination is not sufficient, spironolactone (Aldactone, Pfizer) may be added. Pfizer's eplerenone (Inspra,) is available for use in heart failure following a heart attack. Deaths from heart failure, however, remain high and there continues to be a need for better therapies.

What's in the development pipeline?

Because heart function and cardiac remodelling involve a great many processes, many approaches are represented in the research pipeline for heart failure. For example, inflammatory cytokines directly reduce the ability of the heart muscle to contract, worsening its pumping ability, but also activate the renin-angiotensin-aldosterone system (RAAS), causing narrowing of blood vessels and increasing the resistance against which the heart must pump. Statins have anti-inflammatory properties and improve the function of the cells lining blood vessels, increasing nitric oxide levels, causing blood vessel relaxation, and inhibiting platelet activation (all changes seen in heart failure), as well as lowering blood lipid levels. AstraZeneca is therefore conducting a Phase 3 study of rosuvastatin (Crestor) in patients with heart failure to see whether it can reduce death rates. Also, Novartis is running a Phase 3 study of its renin inhibitor aliskiren in heart failure, since it affects the first step in RAAS activation and may therefore slow remodelling more effectively than ACE inhibitors or ARBs, which act later.

Compounds affecting other processes that are under study at the Phase 2 stage include:

- inhibitors of adenosine A1 receptors (KW 3902, NovaCardia) and SLV320 (Solvay), which may protect kidney function during diuretic therapy
- the thyroid hormone analogue 3,5-diiodothyropropionic acid (DITPA, Titan Pharmaceuticals) which improves cardiovascular function
- glucagon-like peptide-1 (AC2592), under study by Amylin for raising exercise capacity
- the calcium-modulating agent MCC-135 (Mitsubishi) to improve heart muscle function
- the endothelin synthesis inhibitor SLV 306 (daglutril, Solvay)
- the $5HT_4$-inhibitor piboserod (SR 207266, Bio-Medisinsk Innovasjon)

Also at Phase 2 is alagebrium (ALT-711, Alteon), which is being developed for use in the less common condition of heart failure with impaired diastolic function. In addition, sanofi-aventis has AVE 8134 at Phase 2 and AVE 9488 in Phase 1 development for CHF.

When the body can no longer compensate for the adverse changes in heart failure, a sudden worsening in condition known as acute decompensated heart failure may develop, requiring hospitalisation. Few medications are available for treating this condition, which is associated with high death rates. Three new agents have now reached Phase 3 trial. Abbott is developing the intravenously administered calcium-sensitiser levosimendan (Simdax) that increases the ability of heart muscle to contract and dilates blood vessels. Otsuka is studying tolvaptan, and Scios has started a Phase 3 study with nesiritide, a peptide that has shown evidence of being able to reduce breathlessness. Following behind these, at Phase 2, are compounds from Neurocrine Biosciences (urocortin 2), PDL BioPharma (ularitide) and Zealand Pharma (the diuretic ZP120), all of which are designed to help reduce fluid retention in the lung.

The longer-term future

Therapies other than medicines may also have a future role to play in CHF. Injections of stem cells from the patient's own bone marrow may, in some cases, help the heart to repair itself. Gene therapy has been used to insert an inhibitor for the enzyme beta-adrenergic kinase into heart cells, enabling them to contract more strongly. However, such approaches are still very experimental.

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CONTRACEPTION AND INFERTILITY

What are contraception and infertility?

Infertility is defined as 'the incapacity of a couple to achieve conception or to bring a pregnancy to term after a year or more of unprotected intercourse'. Contraception is the opposite: the prevention of conception by physical, behavioural, or medicinal means.

Who does infertility affect?

One in six couples face infertility problems at some point in their lives. Exclusively female or male problems account for 35 per cent each, 25 per cent are due to problems in both partners and 5 per cent remain unexplained. Advances in this field now mean that around half of these couples can be successfully treated.

Present treatments and shortcomings

Hospital and institute-based research in Britain have made a valuable contribution to infertility treatment. For example, IVF (*in vitro* fertilisation) was pioneered by Professors Steptoe and Edwards at the Bourn Hall clinic near Cambridge.

Fertility medicines are used when there is a hormonal defect that inhibits ovulation. If low levels of natural hormone are produced, a woman may be prescribed clomiphene (Clomid, sanofi-aventis), an oestrogen antagonist, for several days in each monthly cycle. This stimulates the pituitary gland to release gonadotrophin, which stimulates ovulation. If this fails or is inappropriate, the individual will be given follicle stimulating hormone (FSH) and human chorionic gonadotrophin (HCG). These mimic the natural hormonal cycle and prepare the woman for ovulation and implantation if the egg is fertilised. The side effects for both types of treatment are relatively mild.

Where infertility has other causes than ovulation failure, such as tubal dysfunction, endometriosis, anti-sperm antibodies or low sperm counts or motility, couples may be offered IVF. Clomiphene and HCG stimulate the ovaries to produce eggs. The eggs are then removed and fertilised *in vitro* and the resulting embryos reimplanted. Success rates are about 20-25 per cent.
Male infertility may be due to erectile dysfunction, low sperm production or defects in the ability of sperm to move (motility) or its maturation. Erectile dysfunction is common in later life and is often due to physical causes such as progressive atherosclerosis or venous leaks, although it may also be related to medication use. The introduction of the phosphodiesterase-5 (PDE-5) inhibitors sildenafil (Viagra, Pfizer), tadalafil (Cialis, Lilly) and vardenafil (Levitra, Bayer) has improved prospects for treating erectile dysfunction, although these are not effective in all cases. Low sperm production may be improved by the use of recombinant follicle stimulating hormone (Gonal-F, Serono) together with chorionic gonadotrophin (Pregnyl, Organon).

Figure 1: **Injection of sperm DNA directly into an egg cell during IVF.**

It is not possible to discuss the many forms of contraceptive medicines here. They fall into three main categories: the progestogen-only pill, the combined pill containing a fixed dose of an oestrogen and a progestogen (the most widely used type), and phased pills, in which there may be two or three kinds of tablet to be taken sequentially each month. Non pill-based contraceptives are also available, such as the etonogestrel (progestogen) implant (Implanon, Organon) that is effective for up to three years and the ethinyloestradiol + norelgestromin skin patch (Evra, Janssen-Cilag). While some concerns linger about the cardiovascular and cancer risk associated with their use, these are very low with modern contraceptives and must be balanced against the risks associated with pregnancy, and the protection against ovarian and uterine cancer that contraceptives can offer.

What's in the development pipeline:

Research continues into improvements in assisted reproduction technology and **infertility** treatment. Organon has a long-acting form of FSH (Org 36286) in Phase 3 trial that will reduce the number of injections needed and Serono has a form of FSH in development at Phase 1. Serono is exploring of anastrozole (Arimidex, AstraZeneca) for ovulation induction in Phase 2 trial.

The field of **female contraception** has also seen advances, even though existing medications have reached a high degree of sophistication. Wyeth has a new combined contraceptive containing levonorgestrel and 17-beta oestradiol and Organon is conducting Phase 3 trials of a new hormone nomegestrol acetate in combination with natural oestradiol.

New compounds are in development for **erectile dysfunction** and related problems. Schering-Plough and Tanabe (TA 1790) are each studying new PDE-5 inhibitors, which have reached Phase 2. Procter & Gamble has continued Phase 3 studies of testosterone skin patches in female hypoactive sexual desire disorder.

FOR FURTHER INFORMATION CONTACT:

Infertility Network UK,
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C

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

What is chronic obstructive pulmonary disease?

Chronic obstructive pulmonary disease (COPD) is a progressive, irreversible restriction of breathing, associated with abnormal inflammation of the lung in response to noxious particles or gases. People with COPD may have chronic bronchitis, emphysema and/or chronic asthma and there is therefore variability in its symptoms. These typically include long-standing cough, sputum production and breathlessness. Smoking is by far the most significant risk factor for developing COPD, followed by exposure to occupational dusts and chemicals and air pollution. A rare hereditary deficiency in alpha-1-antitrypsin may lead to the development of emphysema, but other genetic factors have not been found to be directly responsible for causing COPD. Although COPD shows a steady progression over years, acute exacerbations, about half of them caused by bacterial infection, are common and worsen the outlook for those affected.

Who does COPD affect and how much does it cost?

Around 80 per cent of people diagnosed with COPD smoke, or have smoked. The disease is mainly diagnosed in middle age, because many people do not go to a doctor until their symptoms (usually breathlessness) become troublesome. This may be only after many years of disease progression. About 900,000 people have been diagnosed in England and Wales, but surveys show that many people with reduced lung function go undetected. The Chief Medical Officer has estimated that as many as three million people in the UK may be affected by COPD.

COPD was recorded as the underlying cause of over 23,000 deaths in England and Wales in 2004, but the total number of COPD-related deaths is certainly larger than this. COPD has been estimated to cost the health service over £800 million per year and to have caused 24 million lost working days a year.

Present treatments and shortcomings

No medication has been shown to halt or reverse disease progression in COPD, and the resulting lung damage is permanent. Treatment is aimed at controlling symptoms in a step-wise approach and preventing acute exacerbations. COPD is classified as mild, moderate or severe according to the degree of airflow restriction. Stopping smoking is vital for all those with COPD and is the only intervention that may slow disease progression. Nicotine replacement therapy (with chewing gum, skin patches, lozenges, etc) and treatment with bupropion (Zyban, GSK) are the two main medical options for stopping smoking and are best used together with behavioural support.

NEW SINCE 2000

2000 - Bupropion (Zyban, GSK) smoking cessation

2002 - Tiotropium (Spiriva, Boehringer Ingelheim)

2003 - Budesonide + formoterol (Symbicort Turbohaler, AstraZeneca)

2003 - Salmeterol + fluticasone (Seretide Accuhaler, Allen & Hanburys)

2006 - Salmeterol MDI (Serevent Evohaler, Allen & Hanburys)

Short-acting inhaled bronchodilators (beta$_2$-adrenoreceptor agonists or anticholinergics) are used to relax the airways on an as needed basis in mild COPD. In moderate disease, long-acting bronchodilators are used instead, either singly or in combination. In more severe COPD, an inhaled long-acting bronchodilator may be combined with an inhaled corticosteroid. Such a combination has been shown to reduce overall death rates significantly and to reduce the number of acute exacerbations.

Figure 1: **Bronchodilators are usually taken by inhalation**

Long-term administration of oxygen may be needed in more advanced COPD and can be effective in preventing the progression of complications such as raised blood pressure in the lungs, as well as in relieving symptoms of breathlessness. Antibiotics are prescribed during acute exacerbations if there are signs of infection. Vaccination against influenza and streptococcal pneumonia is also recommended, especially in the elderly, and has been shown to reduce death rates.

Pulmonary rehabilitation - a programme of gentle exercise training and advice on lung health and living with COPD - is helpful for many people with moderate to severe breathing difficulties. It is usually run on an outpatient basis by a hospital, although not all hospitals are yet able to provide it. With the help of trained health professionals, participants are able to increase their activity levels, cope better with breathlessness and gain more control over their condition. They will be encouraged to continue exercising after completing the programme. Rehabilitation can also reduce the risks of hospital admission and death associated with acute exacerbations of COPD.

Figure 2: **Exercise-based pulmonary rehabilitation has significant benefits in COPD**

The short-acting beta$_2$ agonists salbutamol (Airomir, IVAX), terbutaline (Bricanyl, AstraZeneca), or the anticholinergic ipratropium bromide (Atrovent, Boehringer Ingelheim) are the usual starting point of therapy in mild COPD. Long-acting agents used in more advanced disease are the beta$_2$ agonists salmeterol (Serevent, GSK) and formoterol (Foradil, Novartis and Oxis, AstraZeneca) and the long-acting anticholinergic tiotropium (Spiriva, Boehringer Ingelheim). Bronchodilators are generally less effective in improving lung function in COPD than in asthma. A fixed combination of short-acting inhaled medications used in mild to moderate COPD is salbutamol + ipratropium (Combivent, Boehringer Ingelheim). The two combination products containing a beta$_2$ agonist and a corticosteroid indicated for use in advanced disease are budesonide + formoterol (Symbicort, AstraZeneca) and salmeterol + fluticasone (Seretide, GSK). In advanced disease not controlled by these inhaled medications, the oral bronchodilator theophylline (Slo-Phyllin, Merck Pharmaceuticals) may be given, but its many interactions with other medicines and high risk of side-effects mean that it is usually reserved for difficult-to-treat cases.

What's in the development pipeline?

Development of new long-acting beta$_2$ agonists and anticholinergics continues. Several new beta$_2$ agonists for potential once-a-day dosing are in development, including indacaterol (Novartis, Phase 3), carmoterol (Chiesi, Phase 2), and several agents in development by GSK (159797, 159802, 597901, 642444 and 678007).

Once-daily anticholinergics in development include LAS34273 (Almirall) in Phase 3 trial and NVA237 (Novartis), at Phase 2. In addition, Novartis has QAT370 at Phase 1 and GSK has compound 233705 in Phase 2. Interestingly, GSK is conducting Phase 1 studies on a compound (961081) that combines the activities of a beta$_2$ agonist and an anticholinergic in a single molecule.

Several new steroids are in Phase 2 development. GSK has compounds 685698 and 799943 in combination with a long-acting beta$_2$ agonist, while Topigen is studying TPI 1020 - a nitric oxide releasing analogue of budesonide. Nitric oxide relaxes smooth muscle, and TPI 1020 has been shown to be superior to budesonide in protecting against narrowing of the airways. In addition, Epigenesis Pharma is studying EPI-12323, which does not provoke the adverse effects associated with glucocorticoids, such as Cushing's syndrome, brittle bones, etc. It has a long duration of action, making it suitable for once-a-day use.

A completely different approach is being developed in studies of inhibitors of the enzyme phosphodiesterase-4 (PDE-4). This enzyme controls the activity of neutrophils, monocytes and macrophages, as well smooth muscle and cells lining the airways, all of which are involved in the damaging inflammatory over-reaction to smoke and dusts seen in COPD. Inhibiting this enzyme should enable inflammation to be reduced. Unlike steroids and beta$_2$ agonists, PDE-4 inhibitors are often given by mouth. Two such inhibitors are at an advanced stage: cilomilast (Ariflo, GSK) has completed trials and roflumilast (Daxas, Nycomed) is in Phase 3 trial. These compounds may provoke some gastrointestinal side-effects, although these mostly decrease after the initial stages of treatment. GSK has an inhaled PDE-4 inhibitor (256066) in Phase 1 trial that may be a suitable alternative. Other PDE-4 inhibitors are being developed by Ono Pharma (ONO-6126, Phase 2), and Forest Labs (Oglemilast, Phase 1).

Other new treatments are based on inhibiting other mediators of the inflammatory response in COPD. Leukotriene B$_4$ and other substances are released during the inflammatory response and can irreversibly damage lung structures. Interfering with such processes, or with the recruitment or function of the inflammatory cells, offers a new approach to treating COPD. Targets include:

- Interleukin-1β (ACZ885, Novartis, Phase 1),
- Leukotriene B$_4$ (amelubant, Boehringer Ingelheim, Phase 2),
- CXCR2 receptors (Schering-Plough, Phase 2)
- Neurokinins (CS-003, Daiichi-Sankyo, Phase 2)
- p38 mitogen-activated protein kinase (681323 and 856553 GSK, Phase 2).

Finally, a variety of new medicines are being developed with the aim of improving the success rate of smoking cessation. Pfizer has varenicline (Champix) and sanofi-aventis's rimonabant (Acomplia) has completed Phase 3 trials. Sanofi-aventis also has SSR 591813

(Dianicline) in Phase 3 trial. GSK has a compound (468816) for this use in Phase 2 study.

Three vaccine-based approaches are also being explored and these have appeared promising in early trials. Celtic Pharma has TA-NIC at Phase 1. Nabi Biopharmaceuticals' NicVAX is expected to enter Phase 2 trial shortly, while the third vaccine, CYT002-NicQb (Cytos Biotechnology), has already completed Phase 2 studies.

The longer-term future

COPD is now the focus of quite extensive research activity, both on smoking cessation and the treatment of its symptoms, but development of a therapy that actually changes the progression of the condition will probably require a more thorough understanding of the very complex processes involved in inflammation. Equally critical are improvements in diagnostic screening that are needed to identify the large number of people who are believed to be affected by COPD but are so far undiagnosed. Nevertheless, prospects for those identified early in the progress of the disease will probably improve significantly as newer therapies become available.

FOR FURTHER INFORMATION CONTACT:

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CYSTIC FIBROSIS

What is cystic fibrosis?

Cystic fibrosis (CF) is the most common fatal hereditary disease in white people. It results from a defect in a single gene that makes a protein called CFTR (cystic fibrosis transmembrane conductance regulator) which controls salt and water transport across the lining of the lung airways. This defect results in the secretion of thick, sticky mucus in the lungs. In addition, almost all people with CF have nutrition problems and many go on to show liver damage and diabetes. In the lung, mucus coats the small airways, resulting in severe coughing, repeated infections and eventual tissue damage. Lifelong daily physiotherapy is required to loosen mucus and ensure that the lungs remain clear. Through attention to improvements in patient care, life expectancy in CF has increased to about 30 years over the past four decades.

Who does cystic fibrosis affect and what does it cost?

CF affects about 1 in 2,500 live births and the Cystic Fibrosis Trust estimates that approximately 7,500 infants, children and young adults in the United Kingdom have the disease. The cost of treatment increases with age and the severity of disease and is driven by hospital admissions for treatment of respiratory infections. A study in 2000 showed that for those mainly treated in hospital these amounted to £22,000 per year, while for those who were mainly treated at home the cost was £13,500 per year.

Present treatments and shortcomings

Treatment of CF is designed to manage acute symptoms and to slow as far as possible the progress of complications such as lung damage. It is optimised to the needs of each individual. Antibiotics are given both to prevent and treat bacterial infections. Two of the newer antibiotics introduced for use in CF are intravenous meropenem (Meronem, AstraZeneca) and inhaled tobramycin (TOBI, Chiron). The combination of these two has been found to be particularly effective against the Pseudomonas bacterium that infects about half of all people with CF and which often develops multiple antibiotic resistance. In addition, vitamins, nutritional support and pancreatic enzyme preparations are given to almost all people with CF. About one third of adults with CF take the enzyme rhDNase (Pulmozyme, Roche) to thin the mucus in their lungs, and a similar number require medication to control their diabetes.

What's in the development pipeline?

Infection control, both treatment and prevention, remains a key aspect in the management of cystic fibrosis. For treatment, Novartis is developing a dry powder inhaler form of tobramycin and this has reached Phase 3 trial, as has an inhaled form of the antibiotic aztreonam lysinate being developed by Corus Pharma, which was previously only available in injectable form.

Figure 1: **A child with CF undergoing physiotherapy to clear the lungs**

Much research has been devoted to developing new treatments to help thin and clear the thick mucus that fills the airways in CF. Mucus thickness depends on sodium, chloride and water secretion from the cells lining the airways. All of these new treatments are now at the Phase 2 stage. They include:

- talniflumate (LOMUCIN, Genaera), which blocks mucus over-production
- the purine nucleotide receptor type 2 (P2Y2R) stimulator denufosol (Inspire Pharmaceuticals)
- the CIC-2 chloride channel-opener SPI-8811 (Sucampo Pharmaceuticals)
- DCF987 (BCY LifeSciences), which facilitates mucus clearance

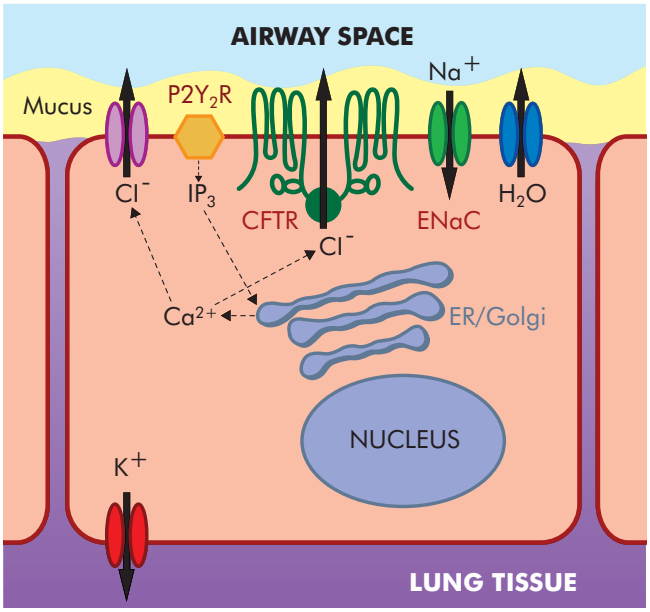

Figure 2: **Some ion channels and receptors affecting mucus thickness in the lung airways.**

Key: Ca^{2+} - Calcium ion; CFTR - Cystic Fibrosis Transmembrane conductance Regulator (a chloride ion channel); ENaC - Epithelial Sodium Channel; ER - endoplasmic reticulum; IP3 - Inosine Triphosphate; K^+ - potassium ion; $P2Y_2R$ - Purine nucleotide Receptor type 2; Na^+ - sodium ion; CL - chloride ion.

- Moli 1901 (Lantibio) that activates an alternative salt channel
- AER 002 (AEROLYTIC, Aerovance) that inhibits the sodium ion channel (ENaC) and increases water excretion
- PTC124 (PTC Therapeutics) that appears to act by helping production of functional CFTR protein.

Other medications in development are enzyme preparations to help improve digestion - r-BSSL, (Biovitrum) and the triple enzyme replacement therapy ALTU 135 (TheraCLEC-Total, Altus Pharmaceuticals) - both of which have reached Phase 2, and DX-890 (depelestat, Debiopharm), also at Phase 2, which is designed to reduce the lung damage that develops later in the disease. Theratechnologies has a growth hormone-releasing factor analogue TH9507 in Phase 1 trial that may help to prevent or reverse muscle wasting.

The longer-term future

Cystic fibrosis has been seen as an ideal test for gene therapy, since restoration of a normal version of the CFTR gene into the lung and digestive system would remedy the underlying defect in CF, with the prospect of curing it. However, although the feasibility of this approach has been shown, improvements have been limited and short-lived and it seems likely that much more fundamental research is needed before this can become a standard therapy.

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DEPRESSION

What is depression?

Unipolar (major) depression is a mental illness involving feelings of sadness, loneliness, despair, low self-esteem and suicidal thoughts. These are frequently accompanied by loss of appetite, concentration, interest and enjoyment, listlessness/lack of energy, sexual dysfunction and sleep problems. Dysthymia is a name used to refer to a milder form of depression that persists for two years or more. Depression is often found together with anxiety (see *Anxiety*). In bipolar disorder (formerly known as manic depression; see *Bipolar Disorder*) there are severe mood swings from high states of agitation to deep despair.

The causes of depression are not well understood and genetic, social, psychological and neurochemical (changes in brain chemistry) factors have all been suggested. There is, however, evidence that *neurotransmitters* in the brain (in particular, serotonin (5HT), noradrenaline (NA) and dopamine (DA), but also others) are significantly affected in depression, and that clinical symptoms can be influenced by medicines that interact with these substances and their receptors. Thus, depression can be distinguished from everyday feelings of sadness. Depression is a real illness, with at least a partly physical basis, and, once correctly diagnosed, can be successfully treated in up to 80 per cent of cases.

Who does depression affect and what does it cost?

Depression affects all ages, but is most common among people between 25 and 44 years old. Major depression carries a significant suicide risk and of 4,000 male suicides in the UK annually, 70 per cent are depressed at the time of their death. It is estimated that more than 2 million people in the United Kingdom are diagnosed as having depression at any one time and many cases may be neither recognised nor treated.

Although there is some evidence of a genetic basis in predisposing to severe depression, this is probably not the case in milder forms. Experiences in childhood are thought to play a role, notably parental neglect and/or physical or sexual abuse. There are also clear gender and social biases: depression is more frequently diagnosed in women and in people who are unemployed, separated, divorced or widowed. Depression is commonly present in some illnesses such as cancer and Parkinson's disease, and a recent report found that half of people with diabetes in the UK also have depression. Post-natal depression affects about 10 per cent of women in the first few months after childbirth.

Depression is the most common cause of admission to psychiatric hospitals in the UK. Cost estimates that include indirect costs, such as lost productivity, sickness and invalidity benefit, put the total societal cost of depression in the region of £9 billion every year. Of that sum, direct treatment costs account for £370 million.

Present treatments and shortcomings

Treatment options for people with depression include anti-depressant medicines and psychiatric and social interventions, such as cognitive behavioural therapy (CBT) and participation in self-help groups. Anti-depressant medicines are not recommended for those with mild depression, whose condition is likely to improve with time without medicines. Anti-depressant medicines are, however, of real value in the management of moderate and severe depression and may be used together with CBT or counselling, if available.

The first medicines for depression to be introduced were the tricyclic antidepressants (TCAs), e.g. clomipramine (Anafranil, Novartis). TCAs are effective in treating the symptoms of depression, but have a relatively wide range of side effects, including dry mouth, dizziness, constipation, sweating and drowsiness, that may discourage patients from persisting with taking them, especially as it may take three weeks or more before their benefit is felt.

More modern anti-depressants have a range of ways of working in the brain, mainly involving neurotransmitters such as serotonin and noradrenaline. The range of medicines available includes:

- **S**elective **S**erotonin **R**euptake **I**nhibitors - SSRIs - such as fluoxetine (Prozac, Lilly), paroxetine (Seroxat, GSK), sertraline (Lustral, Pfizer) and citalopram (Cipramil, Lundbeck)
- **S**erotonin and **N**oradrenaline **R**euptake **I**nhibitors - SNRIs - such as venlafaxine (Efexor, Wyeth)
- selective **N**or**A**drenaline **R**euptake **I**nhibitors - NARIs such as reboxetine (Edronax, Pfizer)
- inhibitors of monoamine oxidase such as moclobemide (Manerix, Roche)

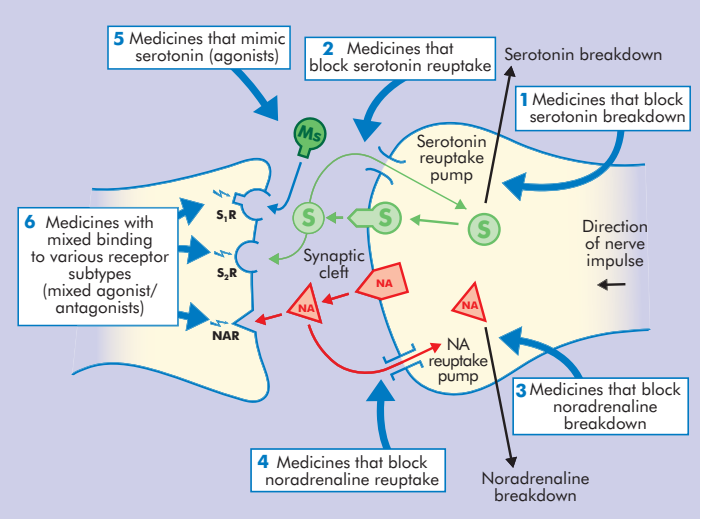

***Figure 1:* Modes of action of common antidepressive drugs on brain synapses.**

Note: although serotonin (S) and noradrenaline (NA) release and receptors are shown here on the same synapse, usually they are on different neurons.

Current guidelines recommend starting anti-depressant treatment with a selective serotonin reuptake inhibitor (SSRI) as these are generally better tolerated than the older TCAs, although they can still cause side-effects (principally nausea, headache and tremor) in some people that can be severe enough to make some patients stop taking them. More recently introduced antidepressants include mirtazapine (Zispin, Organon) which enhances the effect of both noradrenaline and serotonin, the SSRI escitalopram (Cipralex, Lundbeck), and duloxetine (Cymbalta, Lilly), a new SNRI.

What's in the development pipeline?

A great many compounds (more than 45) are undergoing clinical trials to evaluate their effectiveness in treating depression. Those discussed below are only a selection of those in clinical trials, chosen to illustrate the variety of avenues being explored.

A significant number of compounds in trial are modulators of the neurotransmitters noradrenaline, serotonin and/or dopamine. **Dual reuptake inhibitors** (5HT/NA) under development include desvenlafaxine (Wyeth, completed Phase 3), Org 4420 (Organon, Phase 2) and F-2695 (Pierre Fabre, Phase 1), while GSK has an extended release version of the dual NA/DA reuptake inhibitor bupropion. **Triple reuptake inhibitors** (5HT/NA/DA) under investigation include DOV 216,303 (Dov Pharma, Phase 2), GSK 372475 (GSK/NeuroSearch, Phase 2), DOV 102,677 and DOV 21,947 (Dov Pharma, both at Phase 1) and Sepracor's S-225289 (also Phase 1). In addition, AstraZeneca has a sustained release form of quetiapine (Seroquel SR) in Phase 3 study and Lundbeck has a new SSRI (Lu AA21004) at Phase 2. While belonging to the same general approach to treatment, these compounds may have differing effects on the individual symptoms of depression,with varying durations of action, dosing frequencies and side-effect profiles.

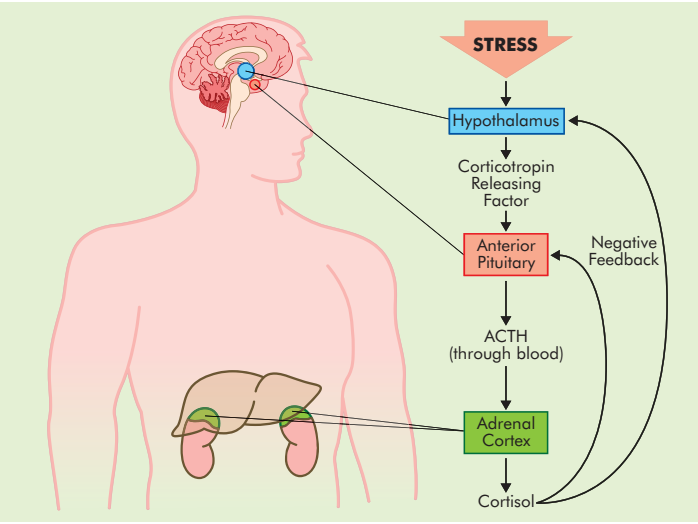

Figure 2: **The Hypothalamic-Pituitary-Adrenal (HPA) Axis and Stress-induced depression. Raised cortisol levels are common in depression, indicating imbalance in the HPA axis.**

Several other families of substances acting in the brain have been implicated in depression, and these avenues too are being explored in the search for new medicines. Receptors for the neuropeptide Substance P (also known as Neurokinin-1) are found widely in brain areas involved in stress responses and anxiety and depression. **NK_1 receptor antagonists** have therefore been seen as prime candidates for medicines for depression and anxiety. However, many such compounds have failed to demonstrate useful clinical effects in earlier trials. Compounds of this type still being investigated include casopitant (GSK) at Phase 2 and GSK 823296, at Phase 1.

A considerable number of other neurotransmitter or neurohormone systems are also being probed for their influence on depression. For example, Servier's agomelatine, in Phase 3 trials for depression, interacts with melatonin (MT_1 and MT_2) receptors as well as $5HT_{2C}$ receptors. Likewise, sanofi-aventis has both a NK_2 antagonist, saredutant, and the beta-3 adrenergic agonist SR 58611 (Amibegron) in Phase 3 trial. At Phase 2, Novartis is studying the benzodiazepine receptor agonist AC-5216, Organon has the glutamatergic AMPAkine Org 24448 (farampator), EPIX Pharma has a combined $5HT_{1A}$ and sigma receptor agonist (PRX-00023), Targacept is working on the selective nicotinic antagonist mecamylamine, sanofi-aventis has a vasopressin-1B receptor antagonist (SSR 149415) and Tetragenex are trialling nemifitide, a melanocyte inhibitory factor-1 antagonist, while many other targets are being explored in Phase 1 studies.

Stress, such as major illness, adverse life events, etc, is a potential trigger for depression. Under stress, the ***hypothalamus*** in the brain produces a locally acting hormone *corticotropin releasing factor* (CRF) which stimulates the pituitary gland to release *adrenocorticotropic hormone* (ACTH) into the bloodstream. Circulating ACTH stimulates the ***adrenal*** glands to release the steroid cortisol, which is known to be able to depress mood. This system, which is known as the HPA-axis, normally regulates itself, as cortisol acts on glucocorticoid receptors in the brain to reduce the production of CRF. Much research is focused on trying to intervene in this complex series of events, with several inhibitors of the type-1 receptor for CRF under study. The most advanced **CRF-1 antagonist** is BMS-562086 (Bristol-Myers Squibb), which has reached Phase 2 trial. The company has two further CRF-1 antagonists in Phase 1 trials (DMP696 and DMP904), but in animal models these have shown greater efficacy against anxiety than in treating depression. Other companies with CRF-1 antagonists are GSK (876008, Phase 2), Ono (ONO 2333Ms), sanofi-aventis (SSR 125543) and Taisho/Janssen (TS-041) all at Phase 1. Organon also has a modulator of the HPA-axis (Org 34517) in Phase 2 study.

The longer-term future

One of the most unsatisfactory features of current antidepressants is that they take several weeks to have an effect, leading patients to stop taking them before their effect is felt. It has been found in a small study in the United States that the anaesthetic ketamine given intravenously is capable of producing an improvement in depressive symptoms within hours. Ketamine itself is not suitable for widespread use as an antidepressant, because of its hallucinogenic properties, but this study finding is important as it shows that it is possible to develop more rapidly acting medications for depression.

Another important recent discovery concerns the way in which the widely used SSRI fluoxetine acts. It has been known for some time that this compound triggers the growth of new brain cells in a region of the hippocampus. It has now been found that fluoxetine acts on a specific type of cell called amplifying neural progenitors. Having discovered this target, it may be possible to investigate it in more detail, and to develop other compounds that have a more potent nerve-cell stimulatory effect, without some of the side-effects of fluoxetine.

Lastly, it is becoming accepted that the category of unipolar depression is probably too broad for one treatment to be effective in all cases. The variations in hormone and neurotransmitter imbalances between individuals are probably considerable, and it may be desirable to develop more nuanced sub-divisions of depression in order to have a higher probability of success by matching antidepressant to a specific sub-category, rather than relying upon observation or experiment.

As yet, these new lines of research are far from delivering new treatments, but, given the intensity of efforts to improve therapy of this widespread condition, it is possible to be optimistic about the future outlook for those affected with depression.

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D

DIABETES

What is diabetes?

Diabetes is a disease in which the body fails to process glucose properly. It is a result either of a failure in the production of insulin, which occurs naturally in the beta cells of the pancreas, or because insulin does not function properly in the organs where it should act. Glucose levels in the blood are too high and, after 5-10 years, complications often arise, with serious personal, medical and economic consequences.

There are two forms of diabetes. **Type 1 diabetes** is an autoimmune disease that is usually diagnosed in the first three decades of life and has been known since ancient times. It is life-threatening if not treated. The second form, **type 2 diabetes**, occurs mostly in middle or later life, although it is increasingly seen in younger people who are obese and sedentary. Type 1 accounts for 10-15 per cent of cases in the UK and type 2 for the rest. There is some tendency for type 2 to run in families, but the pattern of inheritance is unclear.

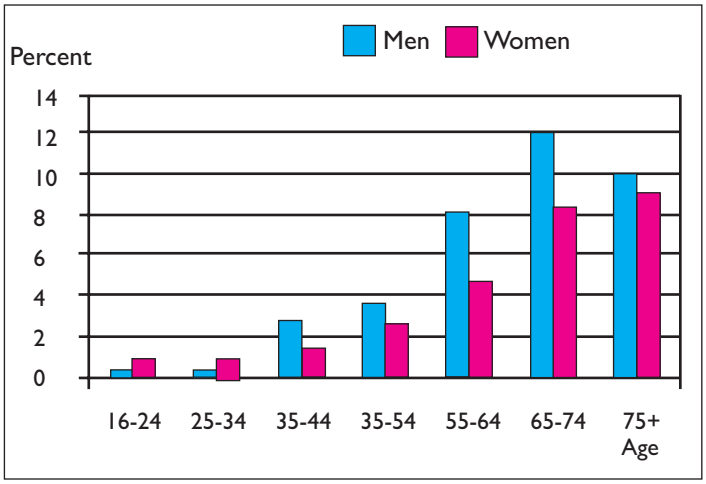

Figure 1: **Prevalence of self-reported diabetes (types 1 and 2) by age**
Source: Health Survey for England, 2003

Who does diabetes affect and what does it cost?

In the UK, diabetes has been diagnosed in more than 2 million people. A further 750,000 are believed to have undiagnosed diabetes. The number affected is growing from year to year, owing to the ageing of the population and the effects of obesity. 5,846 deaths in England and Wales were directly attributed to diabetes in 2004, but it also substantially increases the risk of heart disease (see *Ischaemic Heart Disease*) and stroke, and is thus indirectly responsible for many more deaths.

The cost to the NHS of treating diabetes has been estimated at £3.5 billion a year in 2002. The cost of treating diabetes, and especially its complications such as kidney disease, was found in one survey to account for 9.4 per cent of total hospital expenditure.

NEW SINCE 2000

2002 - Insulin Glargine (Lantus, sanofi-aventis)

2004 - Insulin Detemir (Levemir, Novo Nordisk)

2005 - Insulin Glulisine (Apidra, sanofi-aventis)

2006 - Inhaled insulin (Exubera, Pfizer)

Present treatments and shortcomings

Before the discovery of insulin in 1921, type 1 diabetes was invariably fatal. People with type 1 diabetes make little or no insulin in their pancreas and depend on insulin injections for survival. Many forms of insulin have been marketed. Some are of animal origin, but in recent years, genetically engineered human insulin has been developed. There are now forms of human insulin available which are long- or short-acting, in addition to the regular insulins. Some are available in specially developed self-inject pens (Lilly, Novo Nordisk, Aventis). Recently an inhaled form of insulin (Exubera, Pfizer) has been authorised for use in both type 1 and type 2 diabetes. Careful choice of insulin type and continuing patient education and support are needed to ensure the best therapy and to avoid accidental hypoglycaemia - low blood sugar levels. Problems with patient compliance are a major reason for failure of diabetes therapy and the development of complications.

In type 2 diabetes, there may be a decline in insulin production, but insulin resistance in the body is more often the cause of disease. Many cope through lifestyle changes (weight loss, exercise), but if this fails, medicines (called *oral hypoglycaemics*)

NEW SINCE 2000

2000 - Rosiglitazone (Avandia, GSK)

2000 - Pioglitazone (Actos, Takeda)

2000 - Gliclazide MR (Diamicron MR, Servier)

2001 - Nateglinide (Starlix, Novartis)

2003 - Rosiglitazone + metformin (Avandamet, GSK)

may be needed. The most commonly used are metformin and the sulphonylureas. Sulphonylureas stimulate insulin release, while metformin reduces glucose production in the liver. A somewhat different treatment, acarbose (Glucobay, Bayer), slows the digestion of carbohydrates when taken with a meal, indirectly reducing glucose surge in the blood. More recently introduced are the 'glitazones' rosiglitazone (Avandia, GlaxoSmithKline) and pioglitazone (Actos, Takeda). These act by reducing glucose output from the liver and causing muscles to burn glucose preferentially, rather than using other energy sources, thus lowering blood glucose levels. Two oral hypoglycaemic medicines that stimulate the release of insulin from pancreatic beta cells in a glucose-dependent fashion have also been launched: nateglinide (Starlix, Novartis) and repaglinide (NovoNorm, Novo Nordisk).

Many people with type 2 diabetes eventually require insulin as maintenance therapy, but their need is not for all their insulin, but for a boost to their existing levels. Though anti-diabetic medications can be life-saving, the condition of people with diabetes may slowly worsen, as they become insulin-resistant, or develop complications which pose further problems. Hence there remains an urgent need for new approaches and new medicines.

What's in the development pipeline?

Three companies have new approaches to **type 1 diabetes** in Phase 2 trial. TolerRx has a monoclonal antibody (TRX4) that blocks the action of the T-cells that attack the insulin-producing beta cells in the pancreas, Diamyd Medical has a vaccine (GAD65) that mimics the beta cell protein that triggers the body's immune system to attack the pancreas, and DeveloGen's DiaPep277 acts on the T-cells that cause beta cell destruction. All of these aim to slow down loss of insulin production by the pancreas.

Interest in new insulins for **type 1 and type 2 diabetes** is focused on new forms that eliminate or lessen the burden of the daily injection routine. Lilly and Alkermes are developing an inhaled form of insulin, and Novo Nordisk is working together with Aradigm Corp on another inhaled form (AERx iDMS). Both are in Phase 3 trial. In addition, Biocon has a form of insulin in Phase 2 trial that can be taken orally and Generex has a spray form (Oral-lyn) at the same stage, while Altea Therapeutics has a skin patch formulation (AT1391) in Phase 1 trial.

Research also continues into new treatments for **type 2 diabetes**. The insulin-sensitising glitazones enhance the action of insulin on its target tissues (fat, liver and muscle cells) without affecting insulin secretion (and without the risk of causing hypoglycaemia, which can be an undesirable side-effect of the sulphonylureas and of injected insulin). They achieve their effect by acting on cellular receptors known as peroxisome proliferator-activated receptors (PPARs). Additional PPAR-gamma agonists are in development, including AMG 131 (Amgen) and rivoglitazone (Daiichi-Sankyo), both at Phase 2, but several types of PPAR agonists are in development that act favourably on lipid levels as well as on glucose processing. PPAR agonists in Phase 2 development include netoglitazone (Perlegen), ONO-5129 (Ono Pharmaceuticals), R1439 (Roche), AVE 8134 and AVE 0847 (sanofi-aventis), while GlaxoSmithKline has GSK 677954 and Wyeth has PPM-204. Further examples in Phase 1 trial are GlaxoSmithKline's GSK 625019 and 376501and AVE 0897 from sanofi-aventis.

COMPLICATIONS OF DIABETES

Blood vessels and heart

- coronary heart disease is 2-4 times higher than normal and accounts for 66-75 per cent of deaths from diabetes
- stroke accounts for 15 per cent of deaths in people with diabetes
- blood clots in the limbs can result in amputation, which is 50-80 times more common in people with diabetes

Eye

- People with diabetes have a 13 times higher chance of blindness than people who do not have diabetes
- diabetes is the leading cause of sight problems in the US and Europe

Kidney

- kidney damage/failure is a problem with prolonged illness

Nerves & brain

- pain or loss of sensation can cause foot problems and ulceration that can lead to amputation
- coma due to excess sugar in undiagnosed diabetes has a 50 per cent mortality rate

Box 1: **Complications of diabetes**

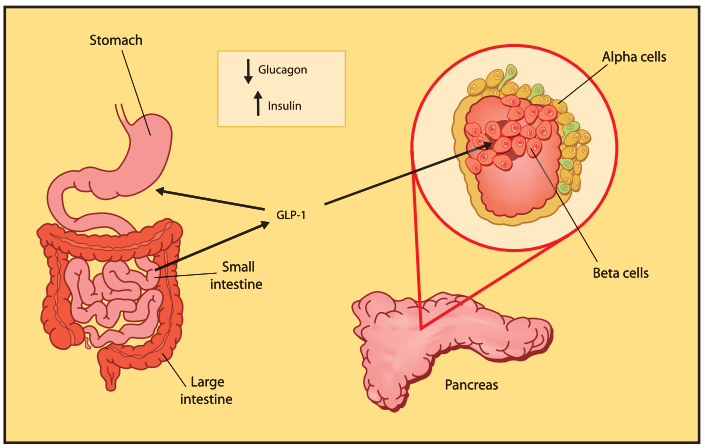

Figure 2: **The peptide hormone GLP-1 readjusts insulin and glucagon release from the pancreas in a glucose-dependent manner in response to eating.**

A different approach to glucose control exploits the ability of the naturally occurring peptide hormone GLP-1 to re-balance insulin and glucagon secretion from the pancreas. This hormone is released from cells lining the small intestine in response to the intake of food. GLP-1 itself is not suitable for therapeutic use, as it is broken down extremely rapidly by the enzyme dipeptidyl peptidase-IV (DPP-IV), but various **GLP-1 analogues** that are resistant to this enzyme are under study. The furthest advanced is exenatide (Byetta, Lilly). This compound has been shown to be able to control blood glucose as effectively as insulin in people with type 2 diabetes and did not exhibit the weight gain often seen with insulin. Liraglutide (Novo Nordisk) is another GLP-1 analogue and this is currently in Phase 3 trial. At Phase 2 are a long-acting form of exenatide, (CJC-1131, ConjuChem), the slow-release GLP-1 analogue BIM 51077/R1583 (Ipsen/Roche), and the GLP-1 receptor agonists AVE 0010 (sanofi-aventis) and albiglutide (GSK).

GLP-1 analogues mostly have the disadvantage that they must be injected; an alternative strategy for controlling GLP-1 level is to find an oral inhibitor of the DPP-IV enzyme that breaks it down so fast. A great number of **DPP-IV inhibitors** are in development, led by vildagliptin (Galvus, Novartis). This is followed at Phase 3 by saxagliptin (Bristol-Myers Squibb and AstraZeneca), sitagliptin (Merck Sharp & Dohme) and SYR-322 (Takeda). Companies with such compounds in Phase 2 trial include Merck Pharmaceuticals (EMD 674992), Pfizer (PF-734200), Phenomix (PHX1149), Prosidion (PSN9301), and Tanabe (TA-6666). Phase 1 compounds are being studied by Alantos (ALS 2-0426), and Lilly (TS-021).

A great variety of other interesting approaches are in research at Phase 2 and earlier, but it is likely to be at least five years before the compounds become available for use.

Complications of diabetes that often develop later in the course of the disease are a major cause of illness and death and pharmaceutical companies are trying to develop compounds to prevent and manage them. For example, disturbances to lipid levels in blood (dyslipidaemia) are common and lead to an increased rate of heart disease (see *Atherosclerosis*). Solvay is developing a combination (Synordia, Phase 3) of fenofibrate and metformin to treat this problem.

Diabetes is a leading cause of **blindness** and Lilly has ruboxistaurin (Arxxant) in Phase 3 trial for this. Also at Phase 3 is pegaptanib (Macugen, Pfizer), currently available for treating age-related macular degeneration, which is being studied in retinopathy, including diabetic macular oedema.

Intractable **pain due to nerve damage** (neuropathy) is another troublesome complication and does not always respond to conventional painkillers. Lilly's serotonin and noradrenaline reuptake inhibitor duloxetine (Cymbalta) has now been indicated for use in this situation and Eisai has ranirestat in Phase 3 trial. GW Pharmaceuticals has a cannabis-based spray (Sativex) under development in Phase 2 trial for this type of pain.

The longer-term future

There are a huge number of new compounds in development for the treatment of diabetes, and this reflects its enormous impact on public health. However, major changes to lifestyle factors such as diet and, especially, exercise will also be needed if the growing burden of diabetes is to be contained.

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Website: www.diabetes.org.uk

EPILEPSY

What is epilepsy?

Epilepsy is a chronic condition characterised by recurrent seizures caused by occasional, excessive and disorderly discharges from nerve cells which spread within the brain (Figure 1). Seizures vary from mild 'absences' through to full-scale convulsions. The seizures can be generalised or partial, affecting only part of the brain. In a few people, they are caused by brain lesions such as tumours or blood vessel abnormality, but in most there is no obvious organic cause.

Who does epilepsy affect and what does it cost?

One person in 20 will have an epileptic seizure at some time in their life. Epilepsy (the tendency to have recurrent seizures) is most often diagnosed in those under 20 years old and those over 60, although seizure frequency seems to decline with increasing age. It is estimated that 450,000 people are affected by epilepsy in the UK, with equal numbers of men and women. No recent figures are available for the costs associated with epilepsy and its treatment in the UK, but earlier surveys have shown that indirect costs (unemployment and raised death rates) account for about 70 per cent of the total.

NEW SINCE 2000

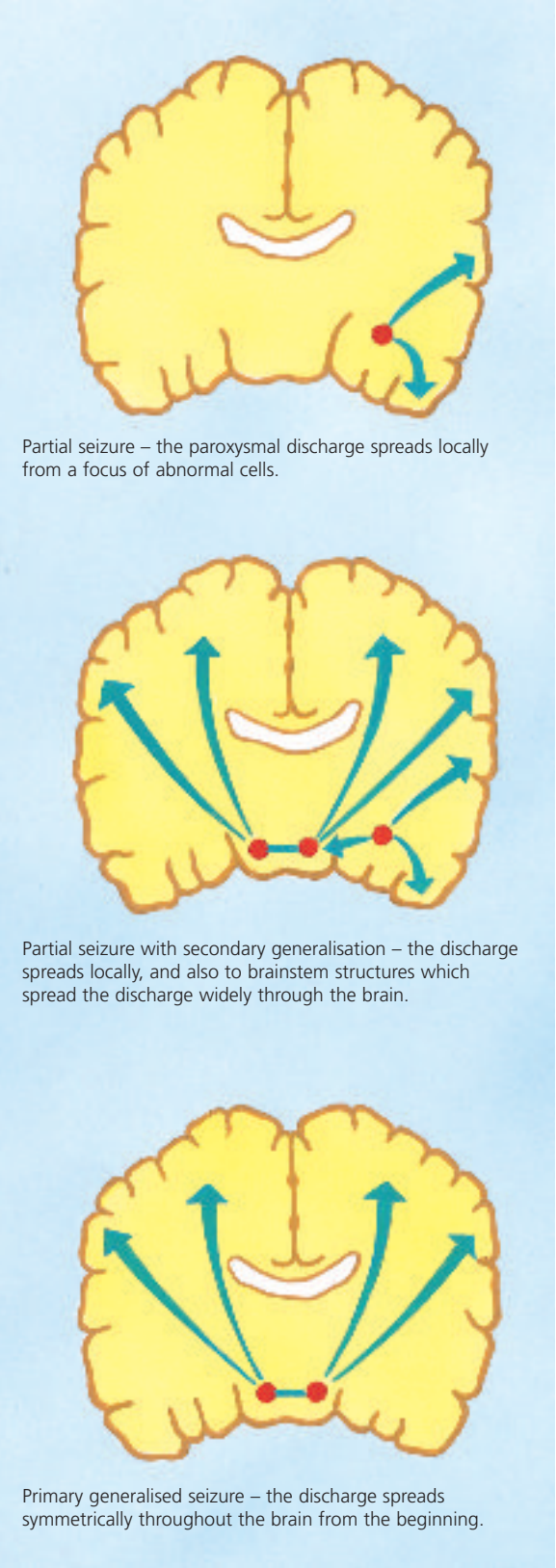
2000 - Oxcarbazepine (Trileptal, Novartis)

2000 - Levetiracetam (Keppra, UCB)

2003 - Topiramate (Topamax sprinkle capsules, Janssen-Cilag)

2004 - Pregabalin (Lyrica, Pfizer)

2005 - Zonisamide (Zonegran, Eisai)



Partial seizure – the paroxysmal discharge spreads locally from a focus of abnormal cells.

Partial seizure with secondary generalisation – the discharge spreads locally, and also to brainstem structures which spread the discharge widely through the brain.

Primary generalised seizure – the discharge spreads symmetrically throughout the brain from the beginning.

Figure 1: **Types of brain discharge in epilepsy**

Present treatments and shortcomings

Some people only have infrequent attacks and medication may not be appropriate, while in others attacks may be much more frequent and incapacitating. About 20-30 per cent of people with epilepsy have more than one seizure per month. A number of medicines have been available for over 25 years, including phenytoin, carbamazepine and sodium valproate, all of which are still in use. These older therapies can control seizures, but almost all cause some drowsiness and other side effects such as nausea, unsteadiness and other side effects. Seizures remain uncontrolled in about half of those being treated. Brain surgery has a role in people who do not respond to current medication, but only about 100 such operations are carried out each year in Britain.

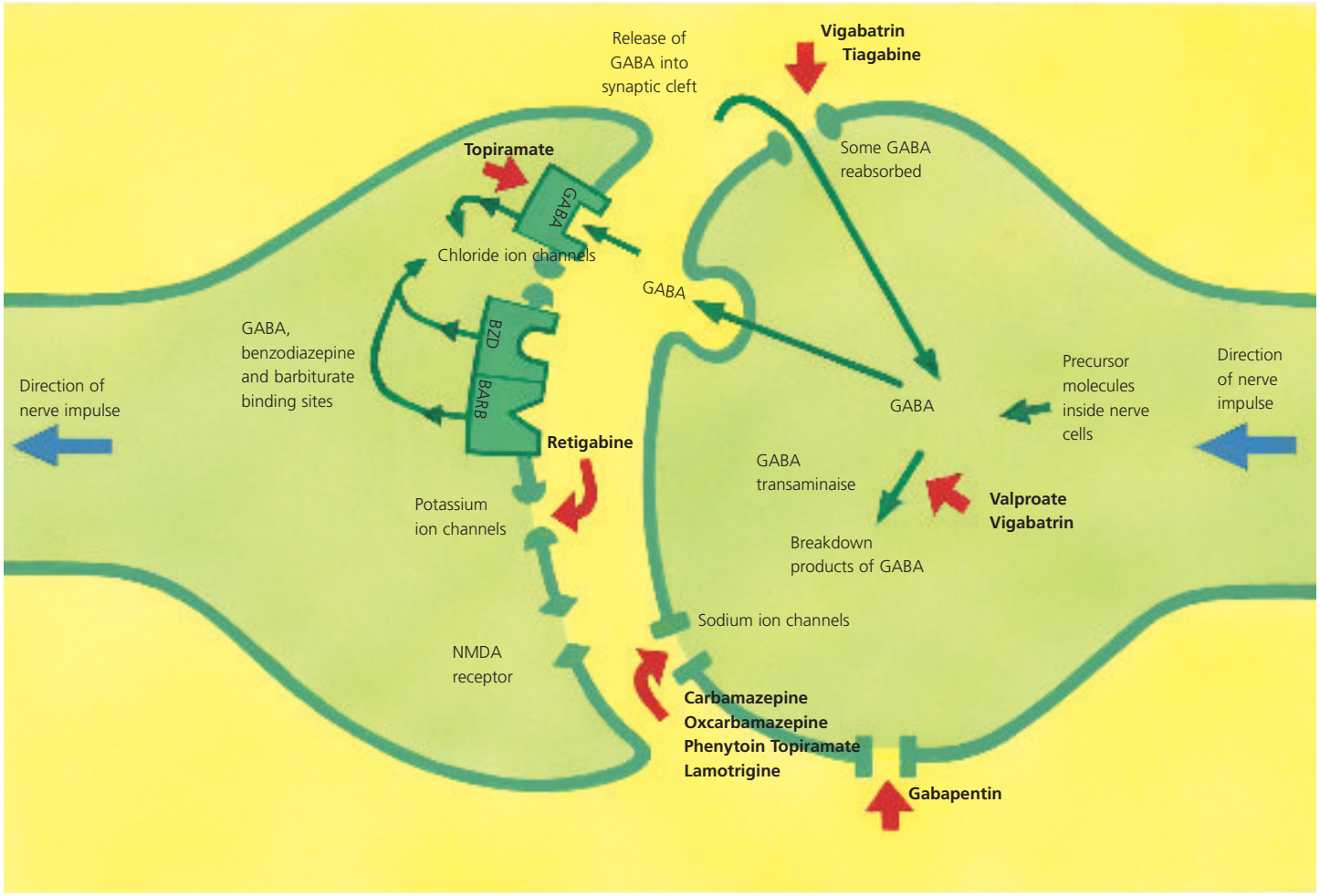


Figure 2: **How some current and developmental anti-epilepsy medicines work**

Many new compounds have been introduced in the last decade. These are: vigabatrin (Sabril, Aventis), lamotrigine (Lamictal, GlaxoSmithKline), gabapentin (Neurontin, Pfizer), topiramate (Topamax, Janssen-Cilag), tiagabine (Gabitril, Cephalon), oxcarbazepine (Trileptal, Novartis), levetiracetam (Keppra, UCB), pregabalin (Lyrica, Pfizer) and zonisamide (Zonegran, Eisai). Lamotrigine, topiramate and oxcarbazepine can be used alone or with other medicines, while vigabatrin can be used alone in infantile spasms and in adults not well controlled on other medicines. All can be used in combination with other medicines.

Therapy usually begins with a single medicine, increasing its dose until the desired control of seizures is achieved. If side-effects become intolerable, another medicine is tried instead. Only when two or three such therapies have been tried and failed is it usual to add a second medicine. Many anti-epilepsy medications need to be taken at least twice a day and side-effects such as drowsiness, dizziness, headache and gastrointestinal symptoms such as nausea are common at first, even with the newer medicines. Only 30-40 per cent of people with epilepsy persist with the prescribed medication in the long term (more than five years) and seizures become intractable in 20-25 per cent.

What's in the development pipeline?

The brain chemistry of epilepsy is complex. The neurotransmitter gamma-amino butyric acid **(GABA)** damps down spontaneous nerve firing that might otherwise trigger an epileptic cascade, and several medicines act by affecting its level, including sodium valproate, vigabatrin and tiagabine. The newer pregabalin is both a GABA modulator and a calcium channel blocker, while Valeant is developing retigabine, which enhances GABA levels by increasing its production, but also acts as a potassium channel opener. Retigabine has reached Phase 3 trial.

A variety of other cellular processes are also targeted in the development of medicines for epilepsy. Several medicines (phenytoin, carbamazepine, lamotrigine, topiramate and zonisamide) act as **sodium channel blockers** and additional compounds of this type are in development. Eisai has developed rufinamide (Inovelon) for use in combination with other medicines and Newron Pharmaceuticals has a sodium channel inhibitor safinamide that has shown efficacy in Phase 2 trial. Meanwhile, GSK is developing an extended release form of lamotrigine, which is in Phase 3.

Levetiracetam is thought to act by preventing neurotransmitter release and also by lowering calcium levels between brain cells. UCB has two more compounds (brivaracetam and selectacetam) in Phase 2 trial that appear to act in a similar way, but appear to show much higher potency, which might lead to better tolerability.

Several companies are exploring the potential of modulators of the amino acid glutamate, in particular so-called **AMPA receptor antagonists**, in epilepsy. Eisai has the compound E-2007 in Phase 2 study and talampanel (Teva) and NS1209 (NeuroSearch) have reached the same stage. The latter compound is being explored for use in emergency treatment of life-threatening continuous tonic-clonic seizures.

Also in advanced clinical development is lacosamide (Schwarz Pharma). This compound is known not to show high affinity binding to receptors for the neurotransmitters adrenaline, histamine, glutamate, dopamine, acetylcholine (muscarinic), GABA, cannabinoids, or serotonin, or to block sodium, potassium or calcium channels. Nevertheless, it has been found in a Phase 3 trial to show efficacy as combination therapy and a further Phase 3 trial is in progress. Lastly, Johnson & Johnson has a compound (RWJ-333369) in Phase 2 trial for combination therapy of partial seizures.

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OR

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F

FUNGAL INFECTIONS

What are fungal infections?

Fungi include both yeasts and moulds. Thousands exist and a few infect humans. Of these, some invade the skin, causing mild infections, such as ringworm and athlete's foot. Yeasts, especially *Candida*, infect the mucous membranes of the mouth and vagina, and cause thrush. *Aspergillus*, *Candida*, *Pneumocystis* and *Cryptococcus* can also invade the body in people with weak or suppressed immune systems (e.g. AIDS, transplant patients, cancer patients) and cause life-threatening infections.

Who do fungal infections affect?

Anyone can pick up minor fungal infections of the skin or nails. But infections requiring hospital treatment, especially invasive candidiasis and aspergillosis, have doubled in the past 15 years to around 4 per 1000 patients. They are the hidden killers, reflecting the increased use of immunosuppressive therapy in cancer and transplantation, which allow infections to take hold more easily. Patients undergoing surgery form the largest at risk group for such invasive infections and a recent analysis has shown that preventive use of an antifungal medication can reduce invasive fungal infections by a half and overall deaths by a quarter.

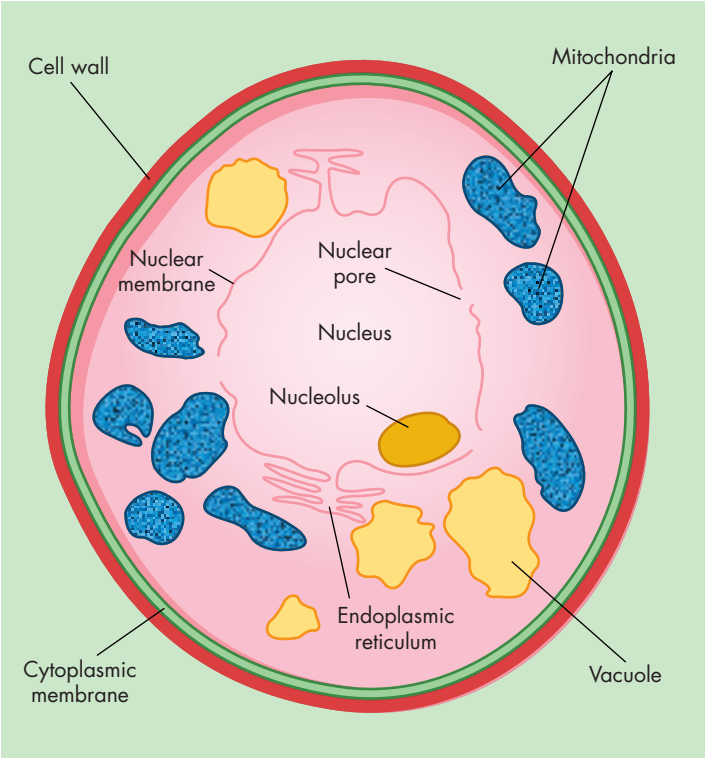

Figure 1: **A cell wall surrounds fungal cells (not present in human cells) and their slightly different metoblism provides targets for antifungal compounds.**

NEW SINCE 2000

2000 - Caspofungin (Cancidas, Merck Sharp & Dohme)

2002 - Voriconazole (VFEND, Pfizer)

Present treatments and shortcomings

One class of powerful antifungal molecules, the **azoles**, hold most of the top ten places for antifungal medicines. They include fluconazole (Diflucan, Pfizer), itraconazole (Sporanox, Janssen-Cilag), and ketoconazole (Nizoral, Janssen-Cilag). They work by blocking the formation of ergosterol, a key component of fungal cell membranes. Fluconazole is able to cure candidiasis with a single oral dose, is active against cryptococcal meningitis in AIDS patients, and also has a role in preventing infection in bone marrow transplant recipients. However, as with bacteria (see *Bacterial Infections*), resistant strains are becoming an increasing problem. Two newer azole antifungals that may help in this respect are voriconazole (VFEND, Pfizer) and posaconazole (Noxafil, Schering-Plough), both of which are indicated for use in invasive fungal infections.

An older medicine with an important role to play in fungal infections is amphotericin B. Abelcet (Zeneus) and Ambisome (Gilead) show less kidney damage and can be given at a higher dose than the conventional formulation. Other oral antifungals include terbinafine (Lamisil, Novartis, also available in topical form) which is used for the treatment of skin and nail infections. Terbinafine acts by inhibiting an enzyme which is involved in the production of ergosterol.

A completely new class of antifungal agents is represented by caspofungin (Cancidas, Merck Sharp & Dohme), which has been developed for the intravenous treatment of invasive aspergillosis and invasive candidiasis and for the treatment of suspected fungal infections in patients with fever who have low levels of white blood cells. Caspofungin belongs to the echinocandin family of antifungals, which block the production of a major component of the fungal cell wall and are effective in killing fungi, rather than just stopping them growing.

What's in the development pipeline?

Further compounds are in development for the treatment of invasive *Candida* infections. Astellas has developed micafungin (Mycamine) and Pfizer's anidulafungin has completed Phase 3 trials. Indevus is also developing aminocandin, but this compound has so far only completed Phase 1 trials.

A completely different approach to systemic candidiasis has been taken by Neutec Pharmaceuticals (now Novartis), whose Mycograb has also completed trials. Mycograb works with amphotericin B in candidiasis and data suggest that it may have activity against *Aspergillus* and against the organism *Cryptococcus*, which causes meningitis in people with AIDS.

In other developments, Basilea Pharmaceuticals has conducted Phase 2 trials of a new broad-spectrum azole (BAL8557) that was active against fluconazole-resistant *Candida*, Novartis has completed Phase 3 studies of the use of terbinafine (Lamisil) cream to treat the scalp infection *tinea capitis* in children, and York Pharma has a topically applied agent (abafungin, Abasol) of a new type, with both antifungal and antibacterial activity, for fungal skin infections.

The longer-term future

With several compounds in development, the range of treatment options, especially for systemic fungal infections, looks set to be greater than for many years. Nevertheless, the constant emergence of resistant strains is a factor that will make necessary continuing efforts to pinpoint the small but distinctive weak points of fungal cells that can be exploited to eliminate them.

HEPATITIS

What is hepatitis?

Viral hepatitis is an infection of the liver. Three hepatitis viruses cause most cases of the disease in the UK. Hepatitis A (HAV) is generally an acute disease that is only occasionally fatal, but hepatitis B (HBV) and hepatitis C (HCV), both transmitted through blood and body fluids, can lead to chronic infections that are a serious health problem. Adults infected by HBV mostly develop an acute infection and subsequently recover, but about 10 per cent develop chronic infection, which can progress to cirrhosis or to a form of liver cancer. Three main classes of HCV are mainly seen in the UK and these differ in their resistance to treatment. Vaccines are available for the prevention of hepatitis A and B, but not for hepatitis C.

Who does hepatitis affect?

The UK is regarded as a low incidence country for all three types of viral hepatitis and many cases are due to the movement of people between Britain and high-risk countries. The number of acute HAV infections reported in England and Wales fell below 1,000 in 2004 and has been declining since the early 1990s. The number of people chronically infected with HBV or HCV is not accurately known, but is estimated at under 1 per cent of the population in each case. However, only a small percentage of cases of HBV and HCV infection are thought to be diagnosed (17 per cent in the case of HCV) and these include some high-risk groups such as intravenous drug users, in whom rate of infection have been found to be significantly higher. Unlike many other countries, the UK does not have a policy of routine infant vaccination against HBV, preferring a selective approach.

Figure 1: **Hepatitis may not have any obvious symptoms and only be detected by blood-testing**

NEW SINCE 2000

2000 - PEG-Interferon alfa-2b (ViraferonPeg, Schering-Plough) Hepatitis C

2002 - PEG-Interferon alfa-2a (Pegasys, Roche) Hepatitis C

2005 - PEG-Interferon alfa-2a (Pegasys, Roche) Hepatitis B

2005 - Hepatitis B vaccine, adjuvanted (Fendrix, GSK) in renal insufficiency

Present treatments and shortcomings

The main therapy for chronic hepatitis B infection is a course of injections with interferon alpha (Viraferon, Schering-Plough) or a long-acting form of interferon alpha (Pegasys, Roche), or oral therapy with an antiviral compound such as lamivudine (Zeffix, GSK) or adefovir dipivoxil (Hepsera, Gilead). Prolonged treatment (e.g. 48 weeks) is needed in both cases for the greatest chance of viral suppression, but there is a risk that resistant viral mutations may emerge with prolonged therapy, and with lamivudine only about a quarter of patients become virus-free within one year. Relapse may occur when treatment is stopped.

The main therapy for chronic hepatitis C infection is a course of weekly injections for 24/48 weeks (depending on the type of HCV) with interferon alpha (ViraferonPeg, Schering-Plough or Pegasys, Roche) given together with the antiviral ribavirin (Rebetol, Schering-Plough; Copegus, Roche).

Interferons often provoke flu-like side effects that may limit their use, and may induce adverse psychiatric events, including depression. Severe adverse psychiatric events (depression, psychoses, hallucinations, aggressive or violent behaviour) have also been recorded with ribavirin. Lamivudine is given at a lower dose for HBV treatment than in HIV infection and is generally well tolerated.

What's in the development pipeline?

Several new antivirals are under development for the treatment of **chronic HBV infections**. Of these, entecavir (Baraclude, Bristol-Myers Squibb) is perhaps the nearest to becoming available in the UK. This compound has been found to give a higher rate of HBV suppression than lamivudine in patients being treated for the first time and to be effective in about 30 per cent of those who had become resistant to lamivudine. Another compound that has

also shown greater efficacy than lamivudine in comparative trial is telbivudine (Novartis). Other antivirals still in clinical trials include tenofovir (Gilead) at Phase 3, valtorcitabine (Novartis), alamifovir (Eli Lilly), pradefovir (Valeant and Schering-Plough) and ANA380 (Anadys), all at Phase 2, and clevudine (Pharmasset) at Phase 1.

Two **vaccines** for the treatment of established HBV infections are under investigation: Oxxon Therapeutics' Hi-8 PrimeBoost HBV vaccine has shown evidence of efficacy in Phase 2 trial, while PowderMed's pdpSC18 vaccine is starting Phase 1 studies. Meanwhile, development of preventive vaccines has continued, with the introductionof the vaccine Fendrix (GSK) for those with kidney problems and trials of another new vaccine HEPLISAV (Dynavax Technologies, Phase 3).

New antivirals are also being developed for **chronic HCV infections**. Taribavirin (Viramidine, Valeant), which is expected to be less likely to cause anaemia than ribavirin, has reached Phase 3 trials in the United States. Novartis is developing valopicitabine (NMC283), which has shown promise in Phase 2 trial of greater efficacy in combination with a form of interferon in the re-treatment of treatment-resistant HCV than ribavirin. Roche has a polymerase inhibitor (R1626) which has now started Phase 2 trials. Also at Phase 2 are two protease inhibitors - SCH 503034 (Schering-Plough) and VX-950 (Vertex), and compounds with other ways of working, such as Pfizer's PF 3491390, Wyeth and Viropharm's HCV-796, the iminosugar UT-231B (United Therapeutics), Migenix's celgosivir, CPG 10101 (Actilon), a T-cell activator from Coley Pharmaceuticals, and a therapeutic vaccine IC41 from Intercell.

The longer-term future

Prospects for improved treatments for chronic Hepatitis C infections look bright, with several promising compounds in the Phase 1 and preclinical pipelines. Gilead and Achillion are investigating GS 9132, an HCV protease inhibitor, and Novelos Therapeutics has NOV-205 in Phase 1 study. Perhaps most excitingly, Novartis Vaccines has two Phase 1 clinical projects ongoing for the development of a vaccine that would protect against HCV. If this were successful, it would be the first preventive vaccine to become available for HCV and could be of great value in preventing further spread of this serious infection.

FOR FURTHER INFORMATION CONTACT:

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Website: www.britishlivertrust.org.uk

HERPES

What are herpes infections?

There are eight known human herpes viruses, classified into three groups. Cold sores, which affect the majority of us, are caused by *Herpes simplex* (HSV) Type 1 (Figure 1); and genital herpes, one of the most common sexually transmitted diseases, is usually the result of infection by HSV-2 (although some cases are due to HSV 1), and chicken pox and shingles are manifestations of *Varicella zoster* infection. Following primary infection, the herpes viruses persist in one or more body cells (nerve cells in the case of HSV-1, -2 and -3) in a dormant form and may be reactivated, either spontaneously or when the immune system is depressed, possibly with more severe consequences than during the primary infection (e.g. shingles). Herpes viruses of the gamma type have been implicated in the development of various cancers, such as Kaposi's sarcoma.

Who does herpes affect?

Most children are exposed to HSV-1 and those who have a cold sore often become carriers and have recurrences. Cold sores are usually trivial, but in people undergoing immunosuppressive therapy, or who have cancer or AIDS, they can be life-threatening. Similarly, in a new-born baby, infection arising from a vaginal sore can be very serious. Until vaccines against *Varicella* became available, chickenpox was a common childhood infection and shingles, frequent in older people, is often accompanied by severe, long-lasting pain.

Present treatments and shortcomings

When it is latent, herpes virus is concealed inside cells, where it is invisible to the immune system. In cold sores, the cells concerned are nerves in the neck, while in genital herpes the virus lodges in the nerves in the lower spine. *Varicella zoster*, which causes chickenpox, hides in clusters of nerves alongside the spine.

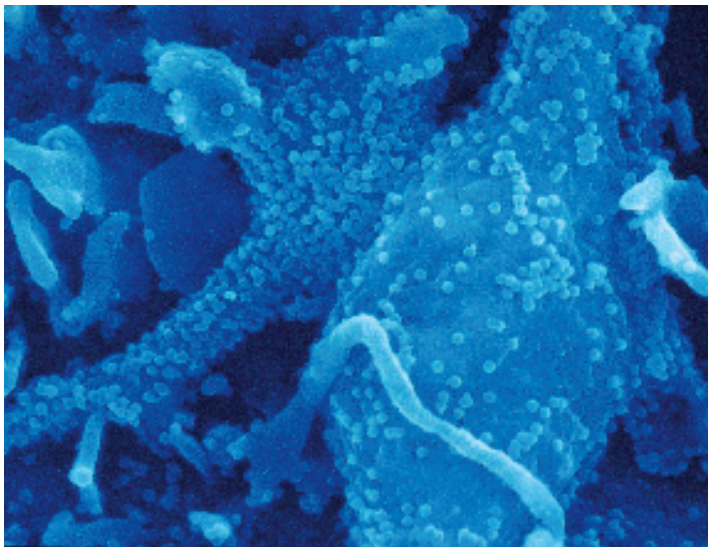

Figure 1: **Herpes viruses escaping from infected cells**

Medical treatment deals with the symptoms, but does not eradicate the concealed virus infection. Milder outbreaks of oral or genital herpes are often treated with non-prescription topical preparations, but more serious or frequently recurring cases require other forms of medication.

Anti-herpes preparations which are available include aciclovir (Zovirax) and valaciclovir (Valtrex) from GlaxoSmithKline, famciclovir (Famvir) from Novartis, inosine probanex (Immunovir, Ardern), and the topical preparations idoxuridine (Herpid, Astellas) and penciclovir (Vectavir, Novartis). Most of these work by blocking replication of the viral DNA, preventing the formation of infectious particles. Ganciclovir (Cymvene, Roche), foscarnet (Foscavir, AstraZeneca) and cidofovir (Vistide, Pfizer), are used for

THE HUMAN HERPES VIRUSES AND THE DISEASES THEY CAUSE

	Type	Common name	Disease associated with virus
HHV-1	Alpha	Herpes simplex, type 1	Cold sores
HHV-2	Alpha	Herpes simplex, type 2	Genital sores
HHV-3	Alpha	Varicella (herpes) zoster	Chickenpox, shingles
HHV-4	Gamma	Epstein-Barr virus	Infectious mononucleosis, Burkitt's lymphoma
HHV-5	Beta	Cytomegalovirus (CMV)	Retinitis, pneumonia (immunosuppressed)
HHV-6	Beta	Human herpes virus 6	Roseola infantum
HHV-7	Beta	Human herpes virus 7	Not known
HHV-8	Gamma	Human herpes virus 8	Kaposi's sarcoma (immunosuppressed)

Table 1: **The human herpes virus and the diseases they cause**

the treatment of cytomegalovirus infections in AIDS and immunocompromised patients. The drawbacks of all of these anti-herpes preparations are the regularity with which they have to be applied, and the fact that they do not eliminate the latent virus from the body.

What's in the development pipeline?

Development projects for herpes virus infections are mainly aimed at *Herpes Simplex*, *Varicella Zoster* and *Cytomegalovirus*. GlaxoSmithKline has its vaccine, Simplirix, in Phase 3 trial for the prevention of genital herpes and PowderMed has a vaccine in Phase 1 study for treating HSV-2 infections. This vaccine produces a response which may enable the virus to be eliminated, or help prevent the viral reactivation that leads to the recurrence of symptoms. Antigenics also has a therapeutic vaccine in Phase 1 trial that is intended to activate both helper and killer T-cells.

Live, attenuated (weakened) vaccines to protect against primary infection with the *Varicella zoster* virus (VCV), and so prevent chickenpox, are already available (Varivax, Sanofi Pasteur MSD; Varilrix, GSK), but Merck Sharp & Dohme's Zostavax has recently been made available for the prevention of virus reactivation in those over 60 who are already carriers and thus at risk of shingles. GSK has a VCV vaccine in development for primary prevention, which has now reached Phase 2 trial. Meanwhile, Janus Pharmaceuticals has a cream containing the antiviral sorivudine in Phase 1 study for the treatment of shingles eruptions and GlaxoSmithKline and XenoPort are developing XP13512 for treatment of the painful post-herpetic neuralgia (nerve pain) that often follows shingles. It is in Phase 2 study.

Cytomegalovirus (CMV) infections are mainly a problem in those with an impaired immune system. Vical is researching a DNA-based vaccine against CMV for the prevention of infections after blood cell transplants and this has reached Phase 2. Sanofi-aventis also has a CMV vaccine in Phase 2 study for prevention of maternal-foetal transmission. Lastly, Viropharma is developing maribavir, a new type of antiviral for the prevention of reactivation of CMV following bone marrow transplantation. It too has reached Phase 2 trial.

FOR FURTHER INFORMATION CONTACT:

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HIV and AIDS

What is AIDS?

AIDS (Acquired Immune Deficiency Syndrome) is the name given to a state arising from infection with the human immunodeficiency virus (HIV, Figure 1). Infection with this virus, a member of a group of viruses called retroviruses, results in destruction of the immune system - especially a group of blood cells called T lymphocytes (T-cells). As the number of T-cells falls, people become increasingly susceptible to infections such as *Pneumocystis carinii* pneumonia - almost unknown in a healthy person. Infections by other organisms that cause disease, such as *Candida*, tuberculosis, cytomegalovirus (CMV) and herpes virus also become more common and serious, even life-threatening. Loss of T-cells also increases the risk of developing some tumours such as Kaposi's sarcoma and non-Hodgkin's lymphoma. It is the emergence of such complications, usually following a long period of HIV infection, that leads to a diagnosis of AIDS.

Since the introduction of the multi-drug regime HAART (Highly Active Anti-Retroviral Therapy) in 1997, the proportion of HIV-infected people going on to develop AIDS has declined markedly and life expectancy has increased. Death rates from AIDS have fallen by 80 per cent and the number of cases of Kaposi's sarcoma and non-Hodgkin's lymphoma has also decreased.

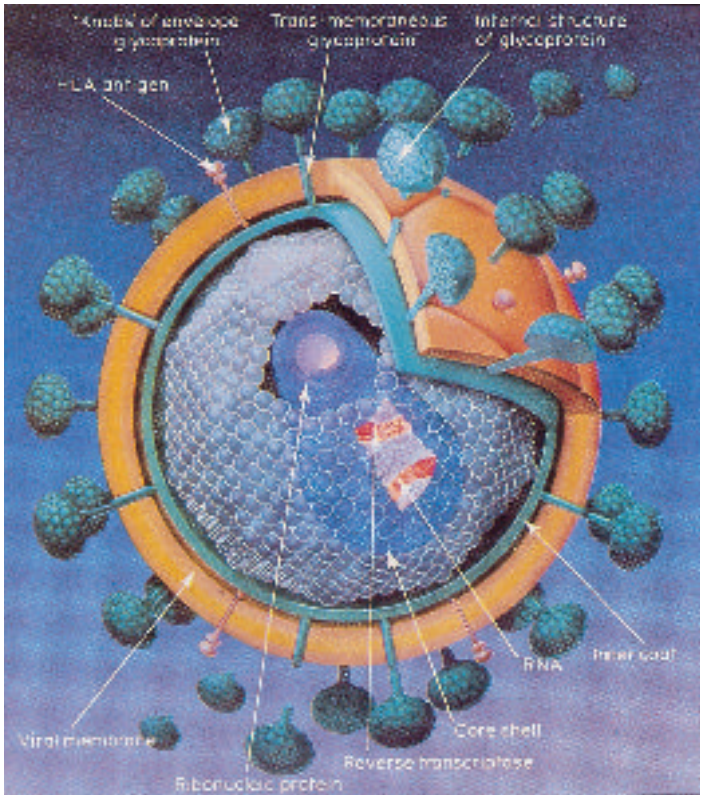

Figure 1: **Structure of an AIDS virus**

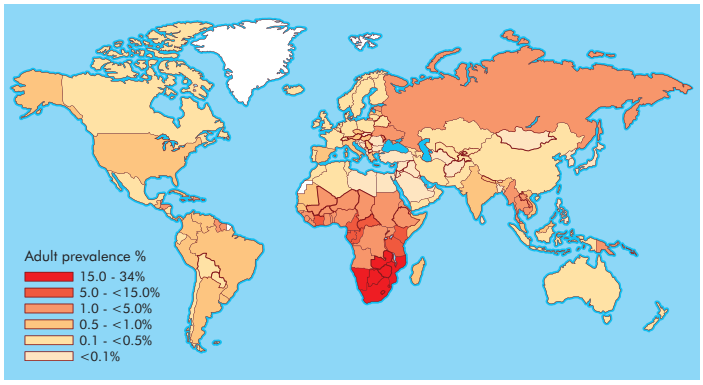

Figure 2: **Global distribution of HIV infection in 2005**
Source: UNAIDS, 2006 Report On The Global Aids Epidemic

Who does AIDS affect and what does it cost?

The World Health Organisation estimates that 38.6 million people had been infected worldwide by the end of 2005, over 4 million of them in 2005 alone. Since it was first recognised in 1981, AIDS has reached epidemic proportions in parts of the developing world, especially sub-Saharan Africa (with an estimated 24.5 million people with HIV/AIDS, 63 per cent of the world total) and south and south-east Asia (estimated 8.3 million).

In the UK, a total of 80,556 cases of HIV infection has been recorded since 1982, with 7,472 new cases in 2004. Almost 22,300 cases of AIDS have so far been recorded in the United Kingdom, with over 16,800 AIDS-related deaths. Heterosexual contact (4,461 new cases in 2004, 53 per cent of the total) has now overtaken sex between men (2,279 new cases, 31 per cent) as the most common route of infection. Three-quarters of HIV infections in heterosexual men and women were probably acquired outside the UK. Currently, about four men become infected for every three women, but this ratio has been declining sharply for several years.

The lifetime cost per patient in the UK was estimated in 2000 at £135,000-181,000. A more recent estimate puts the cost of treatment at around £16,000 per person per year and the total cost of care in 2002-2003 has been estimated at £345 million.

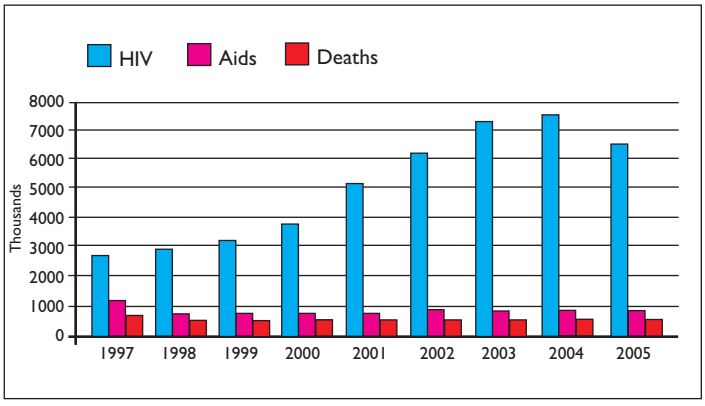

Figure 3: **Yearly new HIV infections, AIDS diagnoses and AIDS-related deaths in the UK since the introduction of HAART**
Source: Health Protection Agency, March 2006. (2005 figures provisional)

Present treatments and shortcomings

Eighteen chemically distinct anti-retroviral compounds are available in the United Kingdom for use in HIV infections (see Table 1). Six of these antivirals are nucleoside inhibitors of HIV reverse transcriptase (NRTI), nine are HIV protease inhibitors and three are non-nucleoside inhibitors of HIV reverse transcriptase (NNRTI). Fixed combinations of some of these compounds are also available.

None of these compounds is, unfortunately, able to eliminate HIV. Used in combination, they reduce the amount of virus in the body, improve immune status and considerably slow down the development of more serious symptoms. The major problems with these medicines are their significant side effects, including damage to nerves and the heart, complicated administration schedules and the development of resistance. Development of once-daily and combination products has reduced the pill burden. However, the development of resistance is still a serious problem. The AIDS virus multiplies very quickly and resistant forms constantly emerge, often within a few weeks of the start of treatment with a new medicine. This extreme changeability of the virus also makes it difficult to design a protective vaccine that could prevent infections.

What's in the development pipeline?

Although nine **reverse transcriptase inhibitors** (RTIs) have already been authorised for use, new antivirals of this type are still being developed. The enzyme reverse transcriptase is central to the route by which the HIV virus spreads to infect new cells and inhibiting it as effectively as possible, and with the fewest possible side-effects, is seen as a key to preventing disease progress.

There are two principal types of medicines that are used to inhibit this enzyme: nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs). New members of both classes continue to be developed, to meet the challenge of resistance and to provide better tolerated, more easily dosed and more effective treatments.

Gilead has developed a one-pill-once-a-day combination of tenofovir and emtricitabine (both NRTIs) with efavirenz, an NNRTI.

Tibotec has two **NNRTI** compounds (TMC 125 and TMC 278) in clinical development. TMC 125 is now in Phase 3 trial, in combination with a protease inhibitor, in patients with resistance to at least one other NNRTI. Statistically significant reductions in viral load after 48 weeks treatment in such patients have been reported for an earlier trial. Meanwhile, TMC 278 has reached Phase 2b trial in patients being treated for the first time. Both compounds have been shown to be active *in vitro* against strains of HIV that have become multiply resistant.

Two other NNRTIs are at an earlier stage of development. Pfizer's UK-453,061 is in Phase 2 trials and Boehringer Ingelheim has a compound (BILR 355 BS) that has reached Phase 1 trial. In addition, Bristol-Myers Squibb and Medivir have recently announced a collaboration to develop the NNRTI MIV-170, which is currently in preclinical research. A greater number of NRTIs is under development, and these are all currently in Phase 2 trial. Achillion Pharma's elvucitabine (ACH-126,443) may permit once-a-day use. Also in Phase 2 study are AVX-754 (Avexa), alovudine (MIV-310, Medivir), amdoxovir (RFS Pharma) and racivir (PSI-5004, Pharmasset).

With nine **protease inhibitors** (PIs) available, new developments are less numerous. However, the compound darunovir (Tibotec) has completed Phase 3 trials. Ambrilia Biopharma is developing another PI (PPL-100), which is in Phase 1 trial.

Compound	Company	Mechanisms of Action		
		Protease inhibitor	NRTI	NNRTI
Abacavir	GlaxoSmithKline		•	
Amprenavir	GlaxoSmithKline	•		
Atazanavir	Bristol-Myers Squibb	•		
Didanosine (ddI)	Bristol-Myers Squibb		•	
Efavirenz	Bristol-Myers Squibb			•
Emtricitabine	Gilead			•
Fosamprenavir	GlaxoSmithKline	•		
Indinavir	Merck Sharp & Dohme	•		
Lamivudine (3TC)	GlaxoSmithKline		•	
Lopinavir	Abbott	•		
Nelfinavir	Roche	•		
Nevirapine	Boehringer Ingelheim			•
Ritonavir	Abbott	•		
Saquinavir	Roche	•		
Stavudine (d4T)	Bristol-Myers Squibb		•	
Tenofovir	Gilead		•	
Tipranavir	Boehringer Ingelheim	•		
Zidovudine (AZT)	GlaxoSmithKline		•	

Table 1: **Anti-retroviral compounds for the treatment of HIV infection available in the UK**

NEW SINCE 2000

2000 - Amprenavir (Agenerase, GSK)

2001 - Abacavir + lamivudine + zidovudine (Trizivir, GSK)

2001 - Lopinavir + ritonavir (Kaletra, Abbott)

2002 - Tenofovir (Viread, Gilead)

2003 - Enfuvirtide (Fuzeon, Roche)

2004 - Atazanavir (Reyataz, BMS)

2004 - Fosamprenavir (Telzir, GSK)

2005 - Tipranavir (Aptivus, Boehringer Ingelheim)

Going beyond these three traditional classes of anti-retroviral compounds that form the basis for current treatment, much research centres on compounds called entry inhibitors that prevent HIV entering its target cells, where it replicates. Each of the three distinct steps of entry - attachment, binding and fusion - can be targeted separately. The first of this type (enfuvirtide, Roche) was introduced in 2003 and is a fusion inhibitor, inhibiting the third stage of entry.

Other compounds in development mainly target the second stage of entry - binding of HIV to receptors (CCR5 and CCR4 receptors) on the target cell. The furthest advanced of these is maraviroc (Pfizer), which is now in Phase 3 trial, followed by AMD-070 (AnorMED), Schering-Plough's vicriviroc and TNX-355 (Tanox), all of which have reached Phase 2. Four more are at Phase 1: the oral TAK-652 from Takeda and INCB9471 (Incyte), and the monoclonal antibodies PRO 140 (Progenics) and CCR5mAb004 (Human Genome Sciences). Research has suggested that people lacking a functional CCR5 receptor are largely resistant to HIV infection and this class of entry inhibitors may be a very valuable addition to current medications.

Bristol-Myers Squibb is taking an alternative approach and has two inhibitors of the first step of HIV attachment - binding of the virus coat protein gp120 to CD4 cell receptor - in development. These are the orally available compounds BMS-488043, in Phase 2 trial, and BMS-378806, at Phase 1. The latter has also been considered in a topical form for prevention of HIV infection.

Some projects are designed to intervene at other stages in HIV replication. Merck Sharp & Dohme is developing an HIV integrase strand inhibitor MK-0518, which prevents the DNA made from viral RNA from splicing itself into the genetic material of the host cell nucleus. This compound has reached Phase 3 trials. Gilead is also developing an integrase inhibitor (GS 9137), which is in Phase 2, as is GlaxoSmithKline's S-364735. In other approaches, Koronis Pharmaceuticals is investigating a compound (KP-1461, Phase 1) that is designed to generate a high rate of mutation that is lethal to HIV survival, while Panacos Pharmaceuticals has a maturation inhibitor at Phase 2 (PA-457, bevirimat) that disrupts processing of a protein, producing defective (non-infectious) virus particles.

Anti-retroviral compounds are intended to prevent disease progression, largely by preventing virus replication. However, they are unable to eliminate the virus completely from the body, even though they are very effective in clearing it from the bloodstream. There is now evidence that HIV can lie hidden in cells in areas like the gut and then re-emerge in infectious form if therapy is stopped, or resistant strains of virus emerge. Eventually, therefore, disease progression to AIDS is likely to occur, although the time period before this happens is now much longer than it used to be.

If AIDS does eventually develop, there is a need for medicines to treat opportunistic infections and other complications. Several new compounds are in development for this purpose. For example, Immtech Pharmaceuticals has an oral antifungal (DB289) in Phase 3 trial for treating *Pneumocycstis carinii* pneumonia. HIV-associated defective metabolism of fat (lipodystrophy) is being addressed by two companies: Theratechnologies has TH9507, an analogue of growth hormone releasing hormone, in Phase 3 trial: Serono has somatotropin for this condition.

The longer-term future

HIV infection continues to spread in both developed and developing countries and there is a great need for a protective vaccine that could help stem the epidemic. There are many projects seeking to develop AIDS vaccines, but a viable candidate has yet to emerge, despite enormous efforts by the major vaccine producing companies and many non-profit organisations. The number of projects is large and many different approaches are being tried. Only a sample of such trials are mentioned here; more details are available on the websites of organisations such as the AIDS Vaccine Clearinghouse (**www.aidsvaccineclearinghouse.org**).

The largest current trial is being conducted in Thailand. This is a Phase 3 study, started in October 2003, using a priming dose of a canarypox-based vaccine from sanofi-aventis that carries HIV genes, and a booster injection of a vaccine from VaxGen. This project is being run in collaboration with the Thai Ministry of Health and the US National Institute of Health (NIH) and the Military HIV Research Program. Having recruited over 16,000 participants, it is expected to continue until 2008.

Merck Sharp & Dohme also has a preventive vaccine (MRKAd5) in advanced trial in North and South America. This uses an **adenovirus** vector carrying HIV genes. This vaccine is designed to stimulate CD4+ T-cells to destroy cells that have been infected with HIV, but does not generate protective anti-HIV antibodies. With a target of 3,000 participants, this study is also expected to run until 2008. The study is a collaboration with the HIV Trials Network (HVTN) and NIH.

At Phase 2, Targeted Genetics and various non-profit organisations are conducting a trial in southern Africa of a vaccine (tgAAC09) that uses an **adeno-associated virus** type 2 vector to carry HIV

Stage	Steps in replication	Drug targets
1	Attachment to CD4 receptor	
2	Binding to co-receptor CCR5 or CXCR4	CCR5/CXCR4 receptor inhibitors
3	Fusion	Fusion inhibitors
4	Reverse transcription	Nucleoside and non-nucleoside reverse transcription inhibitors
5	Integration	Integrase inhibitors
6	Transcription	
7	Translation	
8	Cleavage of polypeptides	Protease inhibitors
9	Viral release	

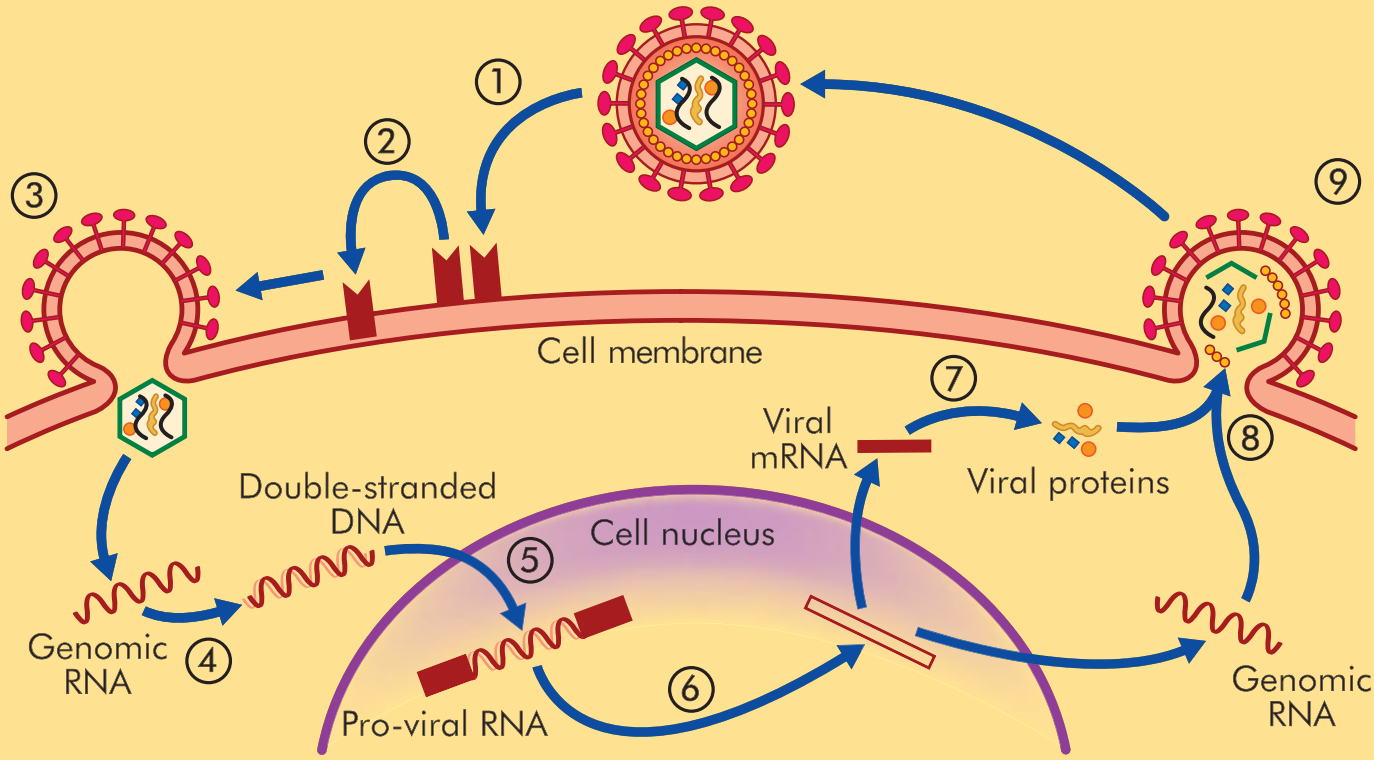

Figure 4: **Life cycle of HIV replication and sites of drug action**
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genes. Also, Vical and GenVec, together with HVTN and others, are testing a **DNA-vaccine**, boosted with an adenovirus vaccine, in a Phase 2 study in the US, Brazil, South Africa, Haiti and Jamaica.

A number of companies are engaged on trials at the Phase 1 stage, including Geovax (DNA-vaccine prime, **modified vaccinia virus** (MVA) booster), Therion (MVA-based vaccine), Novartis (micro-particle vaccines), Pharmexa-Epimune (recombinant protein vaccine), Wyeth (several projects), Alphavax (**Venezuelan equine encephalitis** vector vaccine), GlaxoSmithKline (recombinant gp120 vaccine) and Oxxon Therapeutics (a therapeutic MVA-based vaccine).

Today, the range of medicines for HIV infection is extensive and the disease is more treatable than it was ten years ago. As a result, life expectancy after HIV infection has increased from about 2-3 years in 1984 to over 10 years today. As a protective vaccine is still a long way from being available, the need for more effective and better tolerated medicines remains and the area is still the subject of intense research.

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The Terrence Higgins Trust,
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OR

Positively Women,
347-349 City Road, London, EC1V 1LR.
Phone: 020 7713 0222 (Helpline)
Website: www.positivelywomen.org.uk

HYPERTENSION

What is hypertension?

Hypertension, or high blood pressure, is often called the silent killer, because most people with hypertension feel well and have no symptoms. During each heart beat, there is a fluctuation in the pressure exerted on the inside of the arteries. The normal maximum (**systolic**) pressure is between 110-140mm mercury (Hg) and the minimum (**diastolic**) pressure is 70-90mm. There is much individual variation in blood pressure, depending on time of day, activity, age, general condition of health, etc, but a consistent reading of greater than 140 for systolic pressure and/or 90 for diastolic pressure is now considered to indicate hypertension, irrespective of age.

Hypertension is classified as being either *essential* or *secondary*. Hypertension is said to be essential if no specific cause can be found for it. Essential hypertension accounts for more than 90 per cent of cases. If untreated, it much increases the risk of stroke, heart attack, heart failure, kidney problems, diabetes, etc (see *Atherosclerosis, Congestive Heart Failure, Diabetes*). Secondary hypertension follows from an underlying disease which may need separate treatment, e.g. kidney disease or hormonal disorders. Hypertension in the circulation through the lung (pulmonary arterial hypertension) is seen in chronic obstructive pulmonary disease (COPD) and has a poor prognosis if untreated.

Who does hypertension affect and what does it cost?

The Health Survey for England has found that about 50 per cent of people aged over 55 have high blood pressure (Figure 1). For adults as a whole, 32 per cent of men and 30 per cent of women have hypertension. Strikingly, in the age range 65-74, about 17 per cent of men and 20 per cent of women are being treated for hypertension but still have a blood pressure above the normal range, and about 30 per cent of both men and women in this age group have hypertension, but are not being treated for it. Amongst those aged 75 or more, 54 per cent of men and almost 63 per cent of women had hypertension that was either untreated or insufficiently treated. Hypertension is a main risk factor for cardiovascular disease of all kinds (stroke, heart attack, angina, etc), which the British Heart Foundation has estimated cost the UK healthcare system around £14.75 billion in 2003, with costs of hospital care accounting for about three quarters of the total. Control of hypertension is therefore a major economic imperative, as well as a medical one.

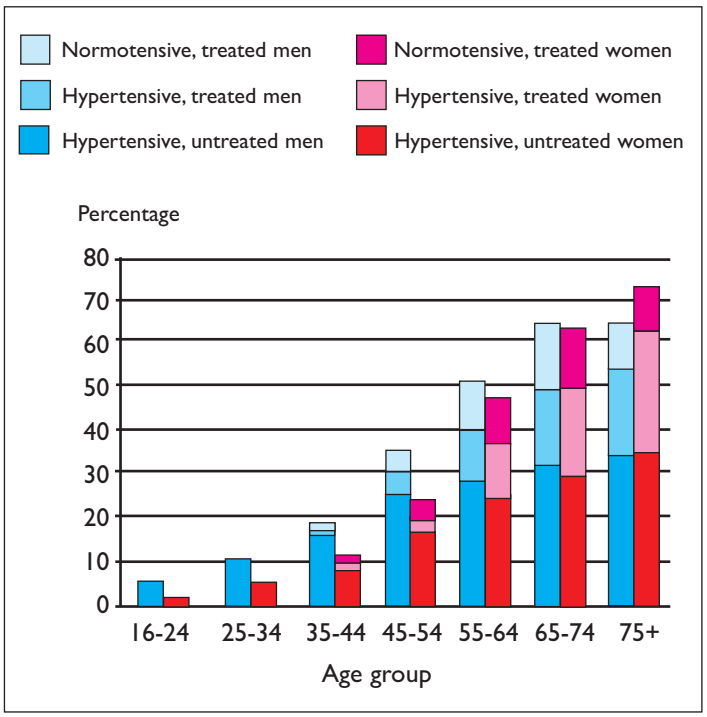

Figure 1: **Prevalence of hypertension (>140/90 mmHg) by age.**
Source: Health Survey for England, 2003.

Present treatments and shortcomings

Antihypertensive medicines fall into eight main classes. Each has strengths, weaknesses and specific applications, and it is not possible to do more here than list the main classes. Following a NICE review, the medicines currently recommended for initial treatment are:

- angiotensin converting enzyme (ACE) inhibitors - they prevent the formation of angiotensin 2 (A-2), a powerful substance that causes narrowing of blood vessels (vasoconstriction) that raises blood pressure
- angiotensin 2 receptor blockers (ARBs) - stop A-2 binding to its receptor site and are recommended if ACE inhibitors are not tolerated
- diuretics - these act by dilating arterial vessels and increasing sodium excretion and urine output, which lowers blood volume and pressure
- calcium antagonists - these inhibit calcium movement into smooth muscles in the walls of blood vessels and the heart, causing muscle relaxation.

No longer recommended for initial treatment, because some evidence suggests that they may lower blood pressure less well than the medicines above and are associated with a raised risk of developing diabetes are beta-blockers, which are classified into those that are heart-selective, those that are non heart-selective, and those that combine beta-blockade with dilating blood vessels. Beta-blockers slow the heart rate and decrease blood output. They are still of value in the management of heart failure and for those who, for example, do not tolerate ACE inhibitors.

Three other types of antihypertensive medicines are used less frequently:

- alpha$_1$ antagonists block nerve impulses that trigger blood vessel constriction
- imidazoline agonists act on receptors in the brain
- central alpha agonists also act in the brain.

Side effects can occur with any antihypertensive medicine, but differ according to the type of medication and the individual. A doctor will take account of a person's age and general condition and the medicine may be changed if it is not well tolerated.

NEW SINCE 2000

2000 - Telmisartan (Micardis, Boehringer Ingelheim)

2000 - Eprosartan (Teveten, Solvay)

2001 - Doxazosin (Cardura, Pfizer)

2006 - Sildenafil (Revatio, Pfizer) Pulmonary hypertension

What's in the development pipeline?

Current medicines can give satisfactory control of blood pressure in many cases, although it may be necessary to use more than one at once. With over 40 compounds in the first five classes of anti-hypertensives listed above, there is a wide choice. However, surveys show that many patients do not achieve target blood pressure levels with existing therapies, perhaps in part due to the need to take several medicines each day, and research into improved antihypertensive medicines continues, as does the development of combinations of existing medicines and dose forms that are easier to take.

New approaches to treatment are less easy to find in such an intensively studied field, but they are possible. Novartis has an orally active renin inhibitor (Aliskiren) which has shown encouraging antihypertensive efficacy in trials, both on its own and when used in combination with other antihypertensives. Aliskiren acts on the same biological system as ACE inhibitors and ARBs (called the renin-angiotensin-aldosterone or RAS system), but it acts at its starting point - the generation of renin - rather than later in the chain of events that, if not inhibited, leads to blood pressure increase.

Other companies are also developing medicines that act in new ways. Myogen has recently started a Phase 3 study of darusentan, a selective endothelin-A receptor antagonist. Endothelin-A binds to receptors in smooth muscle and causes narrowing of the blood vessels, so inhibiting its action should block this blood pressure-raising process. Protherics has a vaccine in Phase 2 study that generates antibodies against angiotensin 2 and thus damps down the RAS system. BioMarin Pharma's oral compound tetrahydrobiopterin, also at Phase 2, stimulates an enzyme to release nitric oxide in the cells lining blood vessels, making surrounding smooth muscle relax and reducing blood pressure. Meanwhile, Solvay is developing daglutril, and sanofi-aventis is developing AVE 7688 (Ilepatril). Both of these compounds have reached Phase 2 trial. Lastly, Speedel has SPP635 in Phase 2 trial that shows prolonged duration of action, which should help ensure 24 hour control of blood pressure.

Development of existing classes of antihypertensive medicines has not stopped. Novartis has Exforge, a once-daily fixed combination of valsartan and amlodipine and Chiesi has developed a fixed dose combination of delapril (an ACE inhibitor) and manidipine (a calcium channel-blocker). Takeda, meanwhile, has TAK-491 and TAK-536, both ARBs, in Phase 2 trial as a possible follow-up to candesartan.

Research is also being devoted to treatments for pulmonary hypertension - a form of secondary hypertension often seen in the advanced stages of chronic obstructive pulmonary disease. The inhaled iloprost (Ventavis, Schering) and the oral bosentan (Tracleer, Actelion) have been the main treatments, but Pfizer has sildenafil (Revatio) available in this indication. Eli Lilly also has its PDE-5 inhibitor tadalafil (Cialis) in Phase 3 trial for pulmonary hypertension. Another new treatment is being developed by Biogen Idec, which has an inhaled form of synthetic vasoactive intestinal peptide (Aviptadil) in Phase 2 trial. Selective endothelin-A inhibitors are being developed by Encysive Pharmaceuticals (sitaxsentan) and GSK/Myogen (ambrisentan), both in Phase 3 trial, while sanofi-aventis has ataciguat (Phase 2), Bayer has BAY 63-2521 (Phase 1) for this indication and EPIX has a $5HT_{2B}$-inhibitor (PRX-08066) in Phase 2 trial.

The longer-term future

Hypertension is such an important health problem that research into new treatments will continue to be lively. As well as the development of new medications, research into better ways of using the various classes of antihypertensive medicines is also important, with attention paid to outcomes other than blood pressure control, such as protection of kidney function and prevention of heart attacks and strokes being a key focus. Several very large long-term trials in such areas are underway and the next decade will certainly see continued, significant progress in the management of hypertension.

FOR FURTHER INFORMATION CONTACT:

The British Heart Foundation,
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OR

The Blood Pressure Association,
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Website: www.bpassoc.org.uk

INCONTINENCE (URINARY)

What is urinary incontinence?

Incontinence is an inability to control the bladder, resulting in involuntary leakage of urine. The processes controlling urination are complex, involving the brain, nervous system and various muscles in the bladder itself. Common types of incontinence are **stress** incontinence (leakage on coughing, laughing, physical exertion), due to physically increased abdominal pressure without detrusor muscle contraction, **urge** incontinence (sudden voiding), as a result of detrusor muscle spasm, **mixed** incontinence, with features of both of the above, and **overactive bladder** (OAB), in which feelings of urgency may cause someone to urinate more frequently without resulting in incontinence. Treatment should address any physical cause of loss of control where possible.

Who does incontinence affect and what does it cost?

The number of people with urinary incontinence is not accurately known, but the Continence Foundation has estimated that as many as 6 million adults in the UK may be affected. Among adults living in the community, women are affected more often than men and are more likely to experience stress incontinence. Overactive bladder accounts for 50 per cent of incontinence in men.

The proportion of people with incontinence increases with age. Cerebrovascular disease (stroke, dementia), impaired mobility and multiple medication are associated with incontinence and it is the most common triggering factor for an elderly person being admitted to residential care. It has been estimated that over half of UK nursing home residents are incontinent.

Incontinence remains a taboo topic and a survey found that of the 14 per cent of men aged 40-79 years who reported continence problems, only 25 per cent had sought medical help. The Continence Foundation has estimated that the cost to the NHS of treating incontinence in England in 1998 exceeded £350 million, of which £23 million were related to medicines and £128 million were for appliances and containment products.

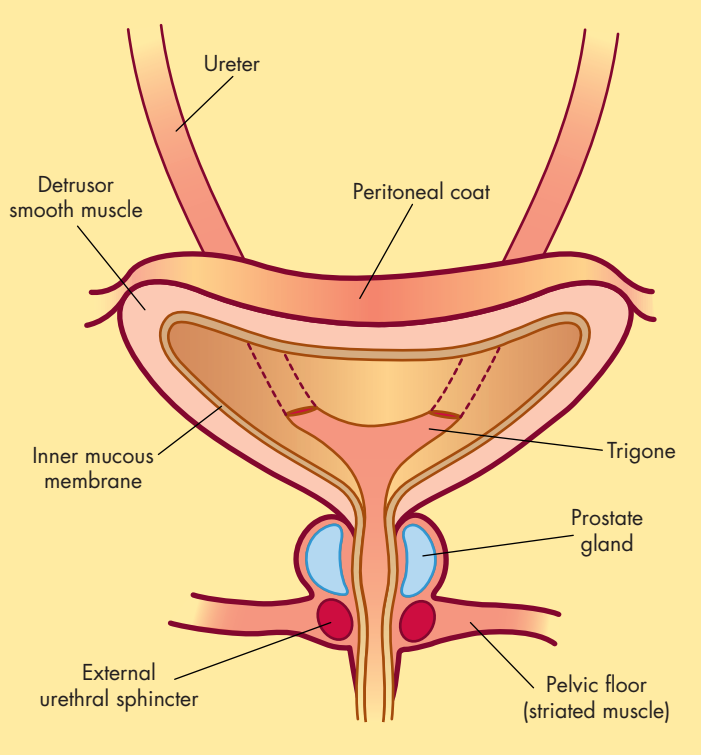

Figure 1: **Anatomy of the bladder (male). Contraction of the detrusor muscle expels urine from the bladder; the urethral sphincter muscle squeezes tight to prevent flow.**

NEW SINCE 2000

2003 - Oxybutinin SR (Lyrinel XL, Janssen-Cilag)

2004 - Solifenacin (Vesicare, Astellas)

2004 - Duloxetine (Yentreve, Lilly)

2005 - Oxybutinin transdermal (Kentera TDS, UCB)

Present treatments and shortcomings

Bladder retraining and pelvic floor exercises help some of those affected but, in addition, medicines acting on the bladder may be helpful. Anticholinergic compounds, such as oxybutynin (Cystrin/Ditropan, sanofi-aventis), propiverine (Detrunorm, Amdipharm), solfenacin (Vesicare, Astellas) and trospium (Regurin, Galen) work on the detrusor muscle of the bladder to reduce spasms by blocking muscarinic receptors of the M3 subtype. They are prescribed for the treatment of overactive bladder and urge incontinence. The alternative anticholinergic tolterodine (Detrusitol, Pfizer) acts selectively on other muscarinic receptors regulating bladder relaxation (M2 receptors). Anticholinergic medicines are helpful but can induce side-effects such as dry mouth, constipation, headaches and, in those with Alzheimer's disease, impaired cognition, so new treatments would be valuable.

Only one medicine is available for the treatment of stress incontinence. This is duloxetine (Yentreve, Lilly), a noradrenaline and serotonin (5HT) reuptake inhibitor. By contrast with muscarinic antagonists, it is thought to act on nerves in the spinal cord that control the urethral sphincter muscle, increasing its tone and thus preventing leakage. Its main side-effects include nausea, dry mouth, constipation, fatigue and insomnia.

What's in the development pipeline?

Darifenacin (Emselex, Novartis) is an M3 selective anticholinergic that is not yet available in the UK. Another anticholinergic at an advanced stage of development is fesoterodine (Pfizer). Other anticholinergics in early clinical research include SMP-986 (Dainippon-Sumitomo, Phase 2) and KRP-197 (Kyorin, Phase 1).

Several new medicines for overactive bladder are under study that act by stimulating the beta-3 subtype of adrenergic receptors. These are found in detrusor muscle, where they are believed to be important for its relaxation, and also in certain other tissues, including the heart and on adipose tissue cells. Companies exploring compounds with this activity are Astellas (YM-178, Phase 2), Boehringer Ingelheim (KUC-7483, Phase 1), GlaxoSmithKline (solabegron, Phase 1) and MediciNova (MN-246, Phase 1).

Another process being explored is inhibition of the type-1 neurokinin (NK-1) receptors found within the spinal cord and in the nerves that control the bladder. These nerves are involved in the impulse that initiates bladder spasm in overactive bladder. GlaxoSmithKline has an agent (casopitant) in Phase 2 trial for overactive bladder that is a specific NK-1 antagonist, as do sanofi-aventis (SSR 240600) and Tanabe (TA-5538).

A variety of other compounds is also being researched. At the Phase 2 stage are elocalcitol (BioXell), DDP200 (Dynogen), two compounds (MK-0594 and MK-0634), from Merck Sharp & Dohme and cizolirtine (Lab. Dr. Esteve). This last compound is also being studied for its usefulness in stress incontinence. Also at Phase 1 are two potassium channel opening compounds, ABT-598 (Abbott) and GSK 366074 (GlaxoSmithKline).

The longer-term future

With this range of new medicines being explored, it seems likely that new compounds will emerge that avoid the side-effects of present anticholinergics. Alternatives to duloxetine for stress incontinence would also be of value. With the ageing of the population, the need for new treatments for urinary incontinence will increase and intensive research seems sure to continue.

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INFLAMMATORY BOWEL DISEASE

What is inflammatory bowel disease?

There are two major forms of inflammatory bowel disease (IBD): **ulcerative colitis** (UC) and **Crohn's disease** (CD). In about 10-15 per cent of cases, it may not be possible to distinguish between them with certainty. The main feature of IBD is inflammation of the lining of the intestine, leading to ulceration, pain, diarrhoea (containing blood in ulcerative colitis) and bowel obstruction (in Crohn's disease). Both diseases are long-term, non-infectious conditions with an unpredictable variation in symptoms over time. They are associated with the risk of anaemia, malnutrition, difficulty in maintaining body salt balance and an enhanced risk of developing bowel cancer. **Irritable bowel syndrome** is a quite different condition, with symptoms including pain and diarrhoea, in which the characteristic tissue damage of UC and CD is not seen.

The causes of IBD are not well understood. In both ulcerative colitis and Crohn's disease, the walls of the gut are found to be infiltrated by inflammatory cells, but the cause of this inflammation is not clearly established in either case. A genetic mutation has been found to markedly increase susceptibility to Crohn's disease (but not to ulcerative colitis). A protein product of this gene is involved in the recognition by cells in the gut of bacteria, and an inappropriate or ineffective immune response to gut bacteria, with migration of inflammatory white blood cells into the cells lining the gut, has been suggested as a cause of Crohn's disease. One bacterium that has been suggested to be involved is *Mycobacterium paratuberculosis*, found in cow's milk and known to cause a similar disease in sheep and cattle. However, the evidence for this infection as a cause of IBD is still unclear. The Australian company Giaconda has a proprietary combination of three antibiotics (Myoconda) in Phase 3 trial in Crohn's disease that may provide a definitive answer to this question. If this disease model were verified, it would be a striking parallel to the way stomach ulcers are caused by *Helicobacter pylori*.

Who gets ulcerative colitis and Crohn's disease and what does it cost?

Ulcerative colitis affects some 120,000 people in the UK and 6,000-12,000 new cases are diagnosed each year. About 60,000 people suffer from Crohn's disease, with 3,000-6,000 new cases a year. The most common age for diagnosis is between the ages of 15 and 25 (CD) to 35 (UC), and men and women are equally affected. No global figures are available for the cost of IBD, but a study found a wide variation in cost per patient. Over six months, the average cost of treating patients with ulcerative colitis was £1,256, while the figure for Crohn's was £1,652. Disease relapse was associated with a 20-fold increase in costs for those needing to be hospitalised.

Present treatments and shortcomings

Management of the acute phase of IBD commonly involves relief of symptoms with antidiarrhoeal medicines, nutritional support and the use of anti-inflammatory steroids, which result in complete or partial remission in about 80 per cent of cases. In addition, Schering-Plough has the anti-TNF-α monoclonal antibody infliximab (Remicade) for treatment of acute CD and for UC that is not controlled by steroids and/or immunosuppressants. In a recent analysis of over 200 patients with moderate-to-severe CD, infliximab treatment was found to be effective in about three quarters of cases, with nearly 80 per cent stopping or reducing steroid use and with a marked reduction in the need for hospital in-patient treatment.

Once acute symptoms have been controlled, the aim is to maintain remission through the use of 5 amino-salicylate derivatives, such as balsalazide (Colazide, Shire), mesalazine (Asacol MR, Procter & Gamble; Pentasa, Ferring, and others), sulphasalazine (Salazopyrin, Pfizer) and olsalazine (Dipentum, UCB). All are available for use in ulcerative colitis, and sulphasalazine and mesalazine are indicated for Crohn's disease as well. Salicylates may also be used for acute treatment in mild to moderate ulcerative colitis, but tend to be less effective than steroids. They can cause nausea, headache and rashes. A Granulocyte Monocyte Adsorption (GMA) apheresis system (Adacolumn, Otsuka) is also available for treating ulcerative colitis that does not respond to steroids. In severe IBD that does not respond to medicines, surgical removal of the diseased segment of the intestine may be necessary.

	ULCERATIVE COLITIS	CROHN'S DISEASE
Parts affected	Rectum and large intestine (colon) only	Any part of the digestive tract from the mouth to the rectum; most commonly the small intestine and/or colon
Areas inflamed	Only the lining of the intestine is inflamed	All layers of the digestive tract may be inflamed, with deep ulceration and scarring of the wall of the intestine

Table 1: **Key differences between ulcerative colitis and Crohn's disease**

What's in the development pipeline?

IBD is a disorder in which inflammatory substances called cytokines, such as tumour necrosis factor alpha (TNF-α), interferon-gamma, interleukin-1 and interleukin-12 are overproduced and can give rise to local tissue damage (Figure 1). Several companies have recognised the potential this provides and the most popular targets for intervention have been TNF-α and IL-12.

UCB has a monoclonal antibody against TNF-α (certolizumab pegol) that is given by monthly subcutaneous injection. This route of administration would permit self-administration by patients whose disease was in a stable phase. In addition, Abbott has adalimumab (Humira) which has completed Phase 3 trials in CD. It has shown efficacy both in induction and maintenance of remission. This antibody is also given by subcutaneous injection.

Approaches targeting IL-12 are at an earlier stage. Abbott has a monoclonal antibody (ABT-874) in Phase 2 trial in CD, as does Centocor (CNTO-1275).

Alpha$_4$-integrins are important in the adhesion of white blood cells to blood vessel walls and their subsequent migration into underlying tissue, where they can contribute to the inflammatory response seen in IBD. Elan has developed natalizumab (Tysabri) that inhibits alpha$_4$-integrin. Trials in people with Crohn's showed a marked decrease in disease activity and a positive response was seen as soon as two weeks after starting treatment. Another integrin inhibitor is in development by Ajinomoto (AJM300, Phase 2).

New formulations of salicylates and steroid derivatives also continue to be developed for IBD. Shire has developed SPD476, a formulation of mesalazine giving delayed and extended release for once-a-day use in mild-moderate ulcerative colitis. Alizyme's ATL-2502 (Colal-Pred) uses a colonic drug delivery system to release the steroid prednisolone locally in the intestine, with the same objective of reducing side-effects. It has reached Phase 3 trial for ulcerative colitis.

The longer-term future

Many other approaches to IBD are in development. Agents under study for **Crohn's disease** include ChemoCentryx's CCX282 and epanova (Tillotts) at Phase 3, while AstraZeneca's AZD 9056 and teduglutide (NPS Pharma) are at Phase 2. Also at the same stage are EGS21 (Enzo Therapeutics), visilizumab (PDL BioPharma), which has reached Phase 3 in ulcerative colitis, and Teva's TV-5010.

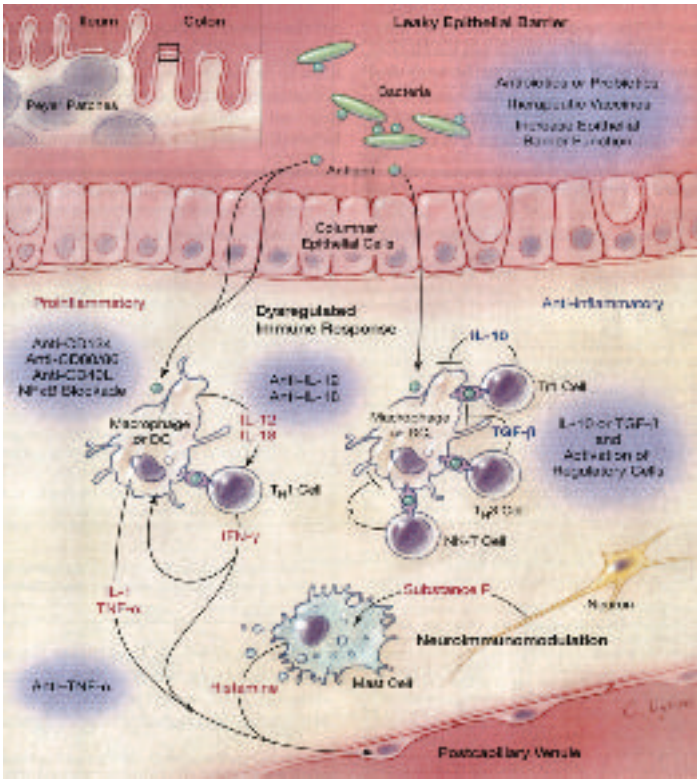

Figure 1: **Induction of an inflammatory response by bacterial antigens leaking across the intestinal epithelial cell barrier**
From Blumberg RS & Strober W, JAMA 2001

Therapeutic targets in **ulcerative colitis** are equally diverse. Otsuka is developing tetomilast, which has reached Phase 3. Pfizer has a monoclonal antibody (PF-547,659) in Phase 2 trial, ISIS Pharmaceuticals has ISIS 2302 and sanofi-aventis has the NK$_1$ antagonist SR 140333 (nolpitantium besylate) at this stage. In addition, Millennium Pharmaceuticals has a monoclonal antibody (MLN02) in Phase 2 study and Medarex has a monoclonal antibody in Phase 1 trial.

Most of the agents mentioned seek to intervene in the immune/inflammatory reaction but the possibility of an infectious origin should not be forgotten. At the very least, with this great diversity of different targets under investigation, it can confidently be expected that management of IBD will improve further in the years to come.

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ISCHAEMIC HEART DISEASE

What is ischaemic heart disease?

Ischaemia is a shortage of oxygen in the blood and fuel to the heart caused by constriction or blockage (*thrombosis*) of the blood vessel feeding it. Ischaemic heart disease (IHD), or coronary heart disease, has two main forms: *angina* and *myocardial infarction*. Ischaemia is usually due to the build-up of plaque (see *Atherosclerosis*) and can affect the brain (see *Stroke*) or muscular tissue such as the legs (see *Peripheral Vascular Disease*), as well as the heart.

A heart attack, or **myocardial infarction** (MI), is an emergency which results when the blood (and hence oxygen) supply to part of the heart is suddenly reduced or stopped. Because the work load on the heart is extremely high, heart muscle deprived of oxygen soon begins to die. Myocardial infarction is most often caused by a blood clot (see *Thrombosis*) lodging in one of the major arteries supplying the heart. A loss of normal heart rhythm (ventricular fibrillation, (see *Cardiac Arrhythmia*) with subsequent circulatory collapse is a significant risk in MI and rapid hospitalisation is required.

Angina is a consequence of a narrowing rather than a blockage of an artery and may be due either to atherosclerosis or, less commonly, arterial spasm. In many people, it is stable over years and only occurs on exertion or exposure to cold, or after a heavy meal; in others, however, it progresses and may occur even at rest. This latter situation is called unstable angina and is serious, as it may be a warning of an impending heart attack.

Who does IHD affect and what does it cost?

The British Heart Foundation estimates that over 230,000 people in the UK had a heart attack in 2004 and that just under 2 million people suffer from angina, with some 345,000 new cases diagnosed each year. In 2004, IHD is estimated to have caused nearly 106,000 deaths in the UK. It was responsible for over 420,000 hospital admissions in England alone. Death rates from IHD have been falling for more than 20 years, as diagnosis and treatment have improved.

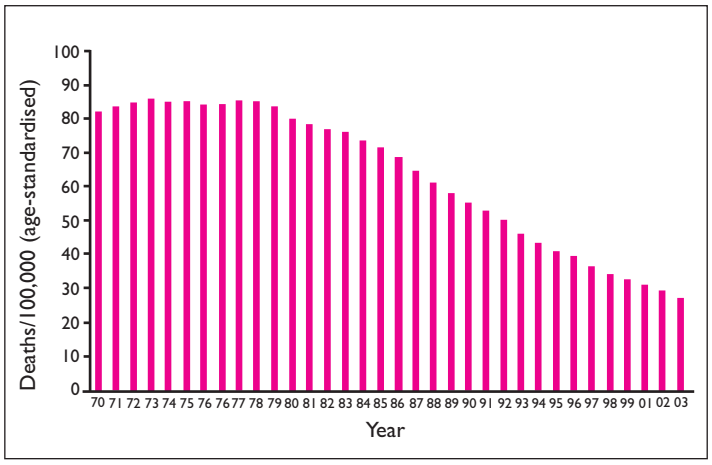

Figure 2: **Death rates from IHD in England in those aged under 65**
[Reproduced with kind permission of the British Heart Foundation]

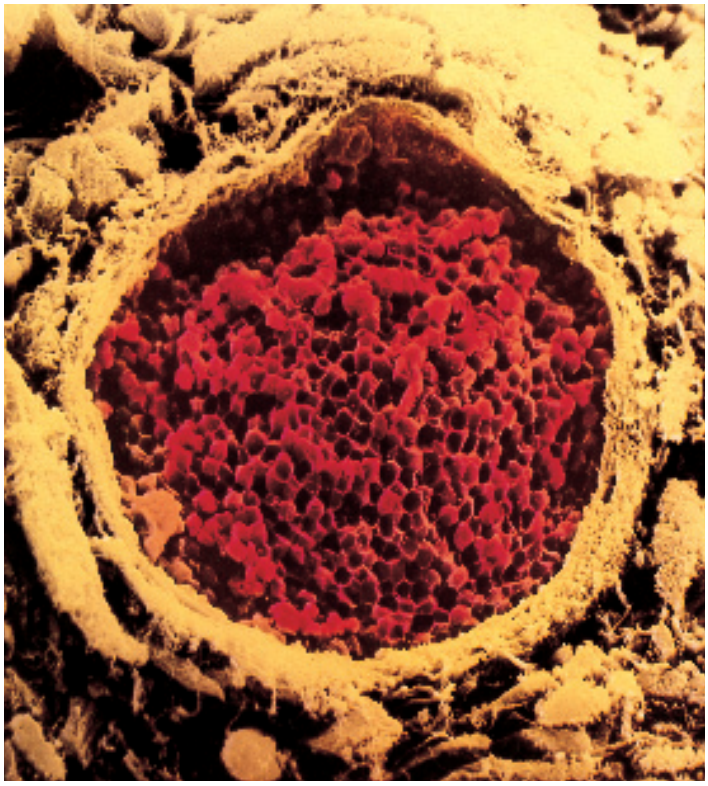

Figure 1: **A blood clot blocking a coronary artery to the heart**

The British Heart Foundation has estimated that the direct cost to the NHS of IHD was £3.5 billion in 2003, of which nearly 79 per cent was due to hospital in-patient costs, with the cost of medications and dispensing them accounting for a further 16 per cent. To this must be added the indirect costs of lost working days and non-professional care in the community, making the total cost to society of IHD an estimated £7.9 billion in that year.

Angina and MI are uncommon below the age of 45, except where there is a strong family history of heart disease, but after that, incidence rises with age. The 2003 Health Survey for England found that 8.2 per cent of men and 4.7 per cent of women in the age range 65-74 had experienced angina in the preceding 12 months and for those aged 75 or over, the corresponding figures were 10.3 per cent and 9.4 per cent respectively.

The risk of IHD can be reduced by modifying lifestyle choices (diet, exercise, smoking), using medication to lower cholesterol and reduce plaque formation (see *Atherosclerosis*), maintaining a normal blood pressure (see *Hypertension*), and through use of anti-platelet medicines such as low-dose aspirin. People with diabetes are especially at risk of heart problems (see *Diabetes*) and vigorous efforts to normalise both blood sugar and blood pressure are necessary.

Present treatments and shortcomings

Treatment of stable angina involves addressing risk factors such as smoking, hypertension and high blood lipids while managing acute

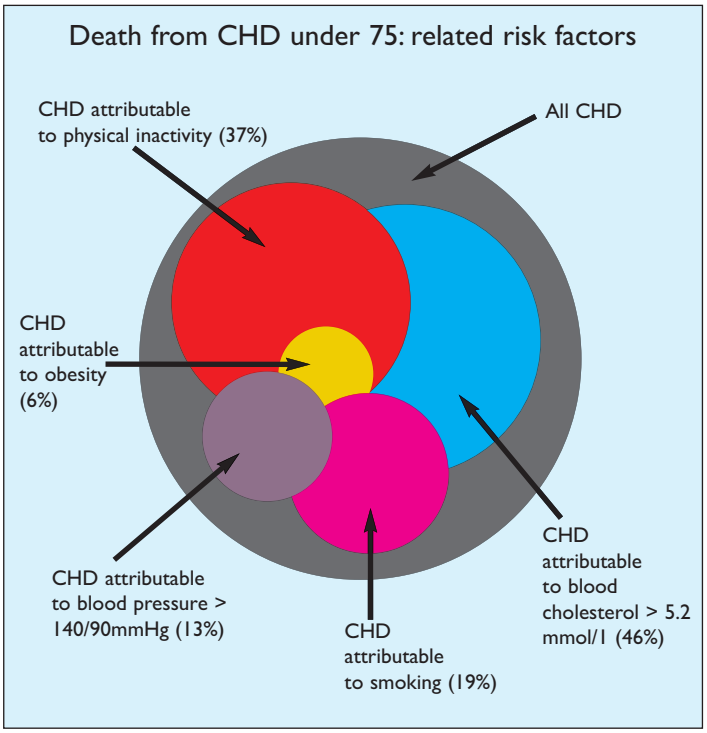

Figure 3: Proportion of all CHD attributable to five different risk factors

symptoms by giving fast-acting glyceryl trinitrate. Unstable angina is a medical emergency and will usually necessitate admission to hospital, as the risk of a myocardial infarction is high.

Longer term preventive treatment of stable angina involves the use of low-dose aspirin or the anti-platelet agent clopidogrel (Plavix, sanofi-aventis) and medicines such as a nitrate, a beta-blocker, or a calcium antagonist, of which there is a large selection available. Slow-release forms of these preparations are often used, or skin patches in the case of glyceryl trinitrate. Tolerance may develop after prolonged use of nitrates and headache is a common complaint on first starting treatment. Both beta-blockers and calcium antagonists may aggravate heart failure and some of these medicines can cause the heart to speed up undesirably.

Surgical treatment may be considered instead of long-term medication and may be preferable in elderly patients. Angioplasty - the use of an inflatable device to widen narrowed arteries - and coronary artery bypass grafting (CABG) are the interventions used. About 62,000 angioplasties were carried out in the UK in 2004 and just under 29,000 CABG operations were recorded in 2002/03.

There are two major aspects in the management of MI - firstly, prevention and, secondly, emergency therapy if a heart attack occurs. Primary prevention consists both of identifying and treating those at especially high risk of IHD, e.g. because of an inherited predisposition, and educating and motivating the public to reduce as far as possible the lifestyle factors linked with the development of IHD. In practice, prevention tends, unfortunately, to mean secondary prevention i.e. prevention of another heart attack once one has already occurred. Thus it represents an attempt to prevent further worsening of already established heart disease.

Prevention of blood clot formation and plaque deposition inside blood vessels (see *Atherosclerosis, Thrombosis* and *Stroke*) is a vital approach to reducing heart attacks and angina. Large studies performed in the mid-1990s showed that cholesterol-lowering statins effectively reduce rates of death, stroke and coronary events when used for secondary prevention. At least part of this effect is as a result of their ability to stabilise existing plaques, as well as lower cholesterol to prevent the formation of new plaque. Treating high blood pressure can significantly decrease stroke, MI and cardiovascular death rates, and some anti-hypertensive medicines such as the ACE-inhibitor ramipril (Tritace, sanofi-aventis) can also inhibit or reverse left ventricular hypertrophy (LVH, a thickening of the heart muscle in response to raised blood pressure that may lead to heart failure) in patients with IHD. A similar effectiveness against LVH has also been found with the diuretic indapamide (Natrilix, Servier) and angiotensin 2 receptor blockers (ARBs) such as candesartan (Amias, Takeda). Thus, medical treatment for secondary prevention after MI might well involve taking a statin, an ACE inhibitor (or an ARB or diuretic) and low-dose aspirin.

Emergency treatment of a heart attack, or unstable angina, involves measures in the first few hours to dissolve the blood clot that is causing ischaemia, re-establishing blood flow to the heart, to prevent or reverse arrhythmias, and subsequently to prevent formation of new clots. (see *Thrombosis*).

What's in the development pipeline?

New modes of action are being explored in the search for improved medications for **angina**. Servier's ivabradine (Procorolan), for use in chronic stable angina, reduces the symptoms of angina by acting to reduce heart rate, thereby reducing oxygen consumption and lessening ischaemia. Astellas has a compound (YM758) with a similar action currently in Phase 2 trial in stable angina. CV Therapeutics has ranolazine, which acts on sodium channels and is at Phase 3 in chronic angina. Cardium Therapeutics is developing a gene therapy approach in an attempt to stimulate the growth of new blood vessels around areas of blockage in chronic angina, improving blood flow to the heart, which is in Phase 3 trial.

Other agents in trial for angina and acute coronary syndrome include prasugrel (Lilly), AZD 6140 (AstraZeneca), fondaparinux (Arixtra, GSK) and enoxaparin (Clexane, sanofi-aventis), all at Phase 3.

Other new approaches are also being explored:

- deCODE genetics is preparing a Phase 3 study of DG031 to prevent plaque rupture and subsequent infarction in unstable angina.
- Sanofi-aventis has ataciguat in Phase 2 trial for chronic angina that may work by relaxing blood vessels and improving blood flow to the heart. The company is also studying SR 123781 and otamixaban in Phase 2 trials for acute coronary syndrome.
- Bayer has BAY 68-4986 in Phase 1 trial to reduce angina.

Re-establishment of blood flow in ischaemia can lead to an inflammatory reaction called reperfusion injury. Activation of the

complement system (part of the body's defence against infection) has been shown to be involved, and Procter & Gamble is studying pexelizumab in Phase 3 trial in myocardial infarction to see if this can reduce death and strokes.

Increasingly, angioplasty includes placing a stent (a small wire tube) inside the affected artery to keep it open. In about 20 per cent of cases, this stent later becomes blocked. Abbott has a stent (ZoMaxx) in Phase 3 trial that continually releases a substance to prevent this blockage.

Medical treatments for **prevention of MI** and other cardiovascular events have now reached the point where advances are mainly being made through the optimal use of existing medications, rather than from the development of new compounds. To determine the best way to use medicines such as ACE inhibitors, ARBs and others requires very large and prolonged clinical studies, and several studies of this kind are taking place.

One of the largest comparative studies showed that a calcium channel blocker was superior to a beta-blocker in terms of preventing stroke and cardiovascular deaths, as well as being less likely to be associated with the development of type 2 diabetes. Findings of this kind have been taken into consideration in the recent revision in treatment guidelines. An even larger trial is comparing the ARB telmisartan (Micardis, Boehringer Ingelheim) with the ACE-inhibitor ramipril (Tritace, sanofi-aventis) and a combination of the two in patients with coronary artery disease or stroke or peripheral vascular disease. When this and other large studies are complete, clinicians will be in a much better position to decide on the best secondary prevention regimen for each individual.

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KIDNEY DISEASE

What is kidney disease?

Any condition leading to restricted blood flow through the kidney can result in damage to kidney tissue. Some medicines may also be toxic to the kidney. **Acute kidney failure** is a sudden decline in kidney function, leading to an increase in concentrations of urea, creatinine and other substances that the kidney normally eliminates from the body. Although often reversible and self-limiting, uncorrected acute kidney failure can be fatal. **Chronic kidney disease** results in a significant reduction in a range of important functions of the kidney. Its causes include high blood pressure, diabetes, inflammation and scarring of the kidney, urinary obstruction and various inherited disorders. It results in the excretion of protein in the urine (albuminuria), and measurement of this can give an indication of disease extent. It eventually progresses, usually over a period of years, to end-stage renal disease (also known as renal failure), which is fatal if not treated by dialysis or kidney transplantation. Weakening of the bones, due to disturbances in calcium, phosphate and parathyroid hormone levels, is a frequent complication of chronic kidney disease.

Who does kidney failure affect and what is the cost?

Kidney Research UK has estimated that around 34,000 people are receiving treatment for kidney failure in the UK, a number that is rising by 8 per cent annually. Around half of them have had a kidney transplant and are receiving anti-rejection treatment, while others are being given regular dialysis, of whom about half undergo peritoneal dialysis and the remainder haemodialysis. There were 1,783 kidney transplants performed in the United Kingdom in 2004/05, with about 6,900 people on the waiting list. The total prevalence of chronic kidney disease may be as much as 50 times that of treated kidney failure, as there may be no obvious symptoms initially and hence it may be undetected in its earlier stages.

Impaired kidney function is more common in the elderly. A study of 50-75 year olds in two London GP practices showed that 6 per cent of those with hypertension also had kidney disease, as did 12 per cent of those with diabetes and 17 per cent of those with both hypertension and diabetes. People of South Asian and African Caribbean origin are 3-5 times more susceptible to kidney disease.

NEW SINCE 2000

2001 - Darbepoetin alfa (Aranesp, Amgen) anaemia in renal failure

2002 - Losartan (Cozaar, Merck Sharp & Dohme) renal protection in diabetes

2005 - Cinacalcet (Mimpara, Amgen)

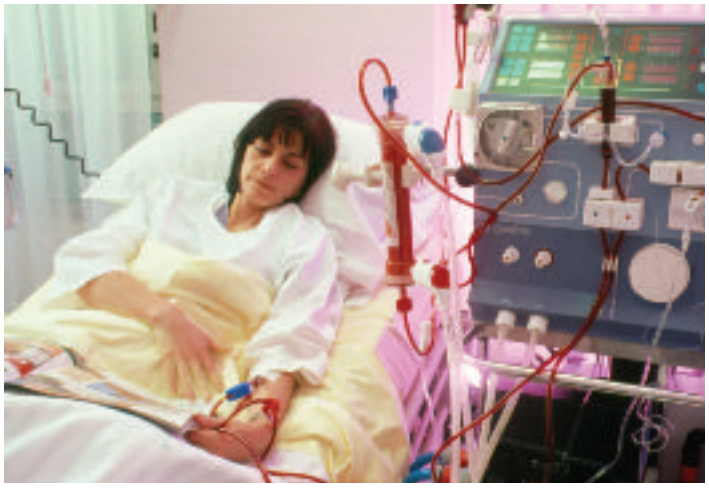

Figure 1: **Haemodialysis to purify the blood in kidney failure is usually carried out in hospital; peritoneal dialysis can often be done by the patient at home.**

Kidney disease represents a significant burden on the NHS budget, estimated at 2 per cent of total spending. The annual cost to the NHS of managing diabetic kidney disease alone has been estimated at £765 million, while the average annual cost of haemodialysis is over £20,000 per patient. The initial cost for transplantation is similar. It is thus very desirable, from both an economic and a humanitarian point of view, to develop ways of preventing the occurrence and progression of kidney disease and to diagnose it early.

Present treatments and shortcomings

In **acute kidney failure**, salt balance has to be maintained with diuretics and vasodilators to allow the damaged kidney time to recover. Established acute kidney failure needs intensive nursing to deal with excess potassium, increasing tissue acidity, possible infection, and problems of nutrition. Dialysis may be necessary, but can be stopped when kidney function has recovered.

In **chronic kidney disease**, many patients will have high blood pressure and/or diabetes and these should be treated. The anti-hypertensive ACE inhibitors and angiotensin receptor blockers (ARBs) have been shown to be able to slow the progress of kidney disease associated with diabetes and hypertension and some are authorised for this purpose. These include the ACE inhibitors captopril (Bristol-Myers Squibb) and lisinopril (Zestril, AstraZeneca and Carace, Bristol-Myers Squibb) and the ARBs irbesartan (Aprovel, BMS/Sanofi) and losartan (Cozaar, Merck Sharp & Dohme). Tight control of blood glucose level is also beneficial for slowing the progression of kidney disease in diabetes (*diabetic nephropathy*).

A low protein diet is used to help control urea levels, and anaemia will be treated with erythropoietin (Eprex, Janssen-Cilag or Neorecormon, Roche) given by injection three time a week, or with a longer-acting variant (Aranesp, Amgen) given once a week. Raised cholesterol levels are very common and are treated using statins to reduce the risk of cardiovascular events such as strokes and heart attacks.

Bone disease caused by kidney disease is treated by reducing blood phosphate level through dietary restriction and with phosphate-binding agents (e.g. Renagel, Genzyme) that prevent absorption from the gut, and by giving vitamin D analogues such as alfacalcidol (One-Alpha, Leo) or calcitriol (Rocalcitrol, Roche) to correct low blood calcium. At the same time, cinacalcet (Mimpara, Amgen) may be given to lower parathyroid hormone levels, which slows down bone breakdown and remodelling.

Regular dialysis or transplantation are used to treat end-stage disease, which is otherwise fatal. Transplantation has been greatly aided by medicines such as cyclosporin (Sandimmun, Novartis), tacrolimus (Prograf, Astellas) and more recently, mycophenolate mofetil (Cellcept, Roche) (see *Transplantation*).

What's in the development pipeline?

A variety of new phosphate-binders are in development. Lanthanum carbonate (Fosrenol, Shire) has completed trials, Mitsubishi's colestilan is in Phase 3, Zerenex (Keryx BioPharma) is in Phase 2 and Ilypsa's ILY101 is in Phase 1.

Roche has developed CERA, which stimulates red cell production and may need to be given only once every 2-4 weeks. Another red cell stimulator in development is AF-37702 (Hematide, Affymax), a synthetic peptide that is in Phase 2 trial. Also under review is oral paricalcitol (Zemplar, Abbott) for control of hyperparathyroidism. Meanwhile AstraZeneca is evaluating whether rosuvastatin (Crestor) can reduce the number of heart attacks, strokes and cardiovascular deaths among those on dialysis.

A diverse range of agents is being studied for use in diabetic nephropathy. At the Phase 2 stage, BioStratum has Pyridorin, Exelixis is trialling XL784, Eli Lilly is studying ruboxistaurin (Arxxant), sanofi-aventis is investigating AVE 7688 (Ilepatril) and Speedel is studying SPP301. At Phase 1 are alagebrium (Alteon) and FG-3019 (FibroGen).

Lastly, there are several treatments being explored for the kidney inflammation (*nephritis*) seen in the autoimmune disease systemic lupus erythematosus. The established immunosuppressant tacrolimus (Astellas) has been developed in this indication, as has Abetimus (Riquent, La Jolla Pharmaceuticals). Abetimus reduces the body's production of antibodies that are thought to be involved in causing this condition. At Phase 3, Genentech is conducting a trial of rituximab (MabThera) GSK has belimumab, licensed from HGS, and Roche is studying mycophenolate mofetil (CellCept) for the same condition.

The longer-term future

The kidney is a complex, vital and sensitive organ. Taking about a quarter of the heart's output of blood at rest, it is intimately connected with the health of the cardiovascular system. In view of the large numbers of people potentially affected by impaired kidney function, it is encouraging that the level of research to provide new medicines in this area is high. Treating kidney disease effectively to reduce progression over time will ease pressure on transplantation and expensive end-stage care such as dialysis.

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LEUKAEMIAS & LYMPHOMAS

What is leukaemia?

Leukaemias are cancers of white blood cells (Figure 1) . Chronic leukaemias may progress slowly over years, but acute leukaemias are much more aggressive and often lead to death within months, or even weeks. Leukaemias are subdivided according to the cell type affected. Examples are **acute lymphoblastic leukaemia** (ALL), **acute myeloid leukaemia** (AML), **chronic lymphocytic leukaemia** (CLL) and **chronic myeloid leukaemia** (CML). Chronic myeloid leukaemia may convert into an acute form, a process known as blast transformation or blast crisis, which is particularly resistant to therapy. Related malignant diseases of the blood cells and lymphoid tissue (**lymphomas**) also include **multiple myeloma**, **myelodysplastic syndrome** (MDS), **Hodgkin's disease** and **non-Hodgkin's lymphoma** (NHL).

Chronic forms of leukaemia cause symptoms such as a tendency to recurrent infections and various signs of immune deficiency. In acute leukaemia, there is an imbalance in the proportions of blood cells owing to infiltration of bone marrow and symptoms may include bone pain and enlargement of organs such as liver, spleen and lymph nodes.

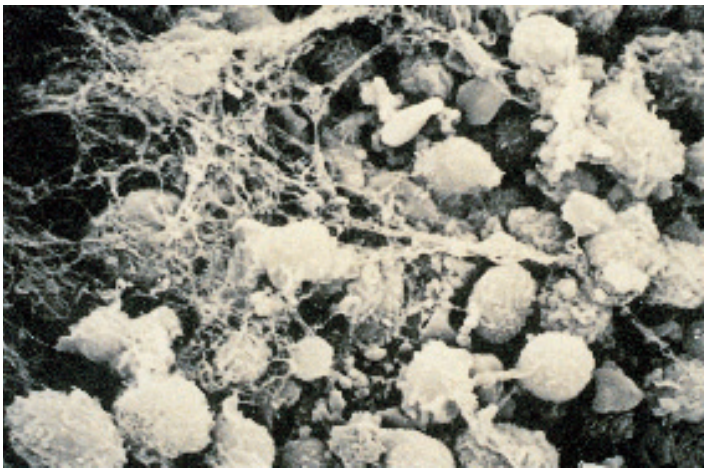

Figure 1: **Normal white blood cells in the bone marrow viewed by electron microscopy**

Who does leukaemia affect?

Leukaemias can occur at any age, but are more common over the age of 50. Each year, about 24,500 people in Britain are diagnosed with some type of blood or lymphoid malignancy, about 6,000 of them with leukaemias (500 cases in children) and nearly 10,000 with lymphomas. NHL is the most common blood cancer (about 8,500 cases per year); some may be associated with HIV infection.

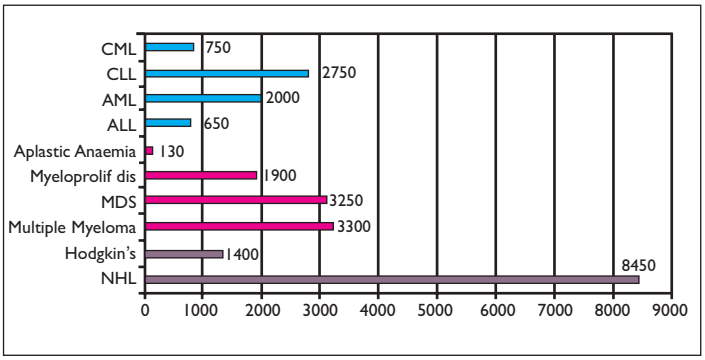

Figure 2: **Average yearly cases of leukaemias, lymphomas and related blood disorders in the UK**
myeloprolif dis = myeloproliferative disorder
Source: Leukaemia Research UK

Present treatments and shortcomings

Leukaemias and lymphomas are more treatable with medicines than most cancers, although remission rates vary considerably from one type to another. Life expectancy is in many cases now much increased. Treatments depend on the type, stage and grade (degree of aggressiveness) of the disease, but generally involve chemotherapy, possibly supported by therapy with naturally occurring proteins called cytokines e.g. interferon or granulocyte colony stimulating factor (G-CSF), and, in some cases, bone marrow or blood stem cell transplantation.

A variety of chemotherapy treatments have been developed that can achieve good remission rates, and specialised cancer centres are constantly refining procedures. In favourable cases, e.g. younger patients with ALL, remission rates may be 80 per cent or more, but eventual relapse remains a problem, due to the difficulty of eliminating all of the malignant cells and the development of resistance. However, in specific situations, such as the treatment of CML with the new agent imatinib (Glivec, Novartis), very high response rates can be achieved, and clinical trial data indicate a significant benefit in survival rate at 42 months after treatment.

During the very intense chemotherapy used to induce remission of disease, and in bone marrow transplantation, side-effects such as bleeding, infections, mucositis, vomiting, liver and kidney damage may limit the doses that can be used, and supportive treatment with a variety of medicines including anti-emetics and G-CSF (Neupogen, Amgen) is given to help minimise these problems.

What's in the development pipeline?

Many new agents are being developed for the various types of leukaemia and lymphoma and only a limited number of selected medicines can be discussed here.

There is a marked need for new treatments for **AML**. Gemtuzumab ozogamicin (Mylotarg, Wyeth) consists of an antibody coupled to the cytotoxic antibiotic calicheamicin. The antibody half of the molecule binds to a protein on the surface of the leukaemic cells, accurately targeting the medicine to its intended goal, to maximise effectiveness and minimise side-effects.

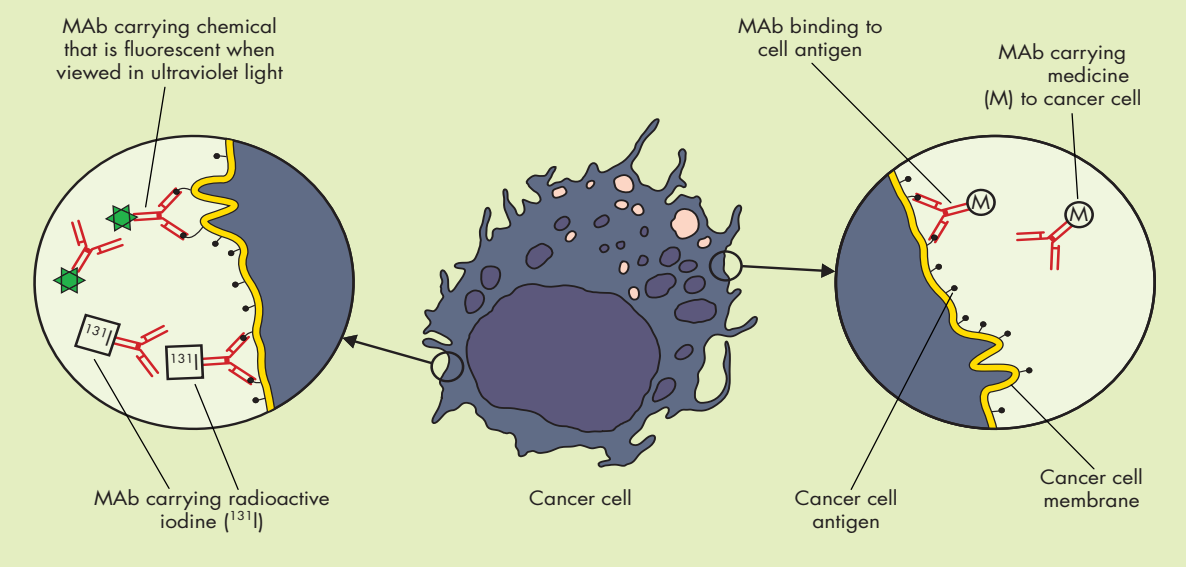

Table 1: **How monoclonal antibodies can deliver toxic molecules to cancer cells**

NEW SINCE 2000

2001 - Imatinib (Glivec, Novartis) CML

2002 - Rituximab (MabThera, Roche) NHL

2003 - Pegfilgrastim (Neulasta, Amgen) neutropaenia post-chemotherapy

2004 - Bortezomib (Velcade, Janssen-Cilag) MM

2004 - Ibritumomab (Zevalin, Schering) NHL

2004 - Alemtuzumab (MabCampath, Schering) CLL

2006 - Palifermin (Kepivance, Amgen) oral mucositis

Also being reviewed is Ceplene (histamine dihydrochloride, EpiCept). When given together with a low dose of the cytokine interleukin-2 (Proleukin, Chiron - only indicated for use in kidney cancer in the UK), this has been shown in clinical trials to lengthen the leukaemia-free survival time in people in first remission from AML. Other new agents under development for treating AML include Cephalon's lestaurtinib, and MGI Pharma's decitabine, both in Phase 3 trial. At an earlier stage, Clofarabine (Evoltra, Bioenvision), an anticancer agent already available for use in childhood ALL, is now in Phase 2 trials, as are XL999 (Exelixis), midostaurin (PKC412, Novartis) and MLN518 (Millennium Pharmaceuticals). Also at Phase 2, Lorus Therapeutics has GTI-2040, SGX Pharmaceuticals has troxacitabine and Vion Pharmaceuticals has a new cytotoxic agent Cloretazine. Although the outlook for adult AML is still poor, the number of new approaches in development is encouraging.

While the introduction of imatinib (Glivec, Novartis) marked a significant advance in treating **CML**, the problem of emerging resistance limits long-term survival and new treatments are still needed. Dasatinib (Sprycel, Bristol-Myers Squibb) has been developed for use in this situation. Also in advanced development is nilotinib (Tasigna, Novartis), that, like dasatinib, has shown high response rates in patients who have become resistant to imatinib. Ceflatonin (ChemGenex) is also being studied for use in these patients and has reached Phase 2 study.

Survival and quality of life are often better in **CLL**, as it often progresses slowly and fewer patients are given chemotherapy than in acute leukaemias. However, those with anaemia or thrombocytopenia have a poorer prognosis and may be treated with chlorambucil (Leukeran, GSK) or fludarabine (Fludara, Schering). There are currently few treatment options for those who become resistant to fludarabine, although the monoclonal antibody alemtuzumab (MabCampath, Schering) has been made available for this situation. Further compounds are however in advanced trial. Sanofi-aventis is exploring alvocidib (Flavopiridol), which has reached Phase 3. Also at Phase 3 are ofatumumab (Genmab and GlaxoSmithKline) and rituximab (MabThera, Roche), and oblimersen (Genasense, Genta).

The most frequent lymphoid malignancy, **non-Hodgkin's lymphoma**, is classified into many different sub-types, according to the cells that each arise from, and these may vary in their response to therapy, making progress more difficult. However, NHL is also the subject of very active research into new treatments. The introduction of the monoclonal antibody rituximab (MabThera, Roche) brought a significant improvement in survival when used together with the standard chemotherapy regimen. Roche has

continued to explore the use of this agent, and it has recently been recommended by NICE for use in first-line treatment of follicular lymphoma (a specific type of NHL).

A further advance occurred when the radio-immunotherapy ibritumomab tiuxetan (Zevalin, Schering) was launched in 2004. This is coupled to radioactive yttrium-90 which destroys the tumour cells. It is indicated for use in B-cell NHL that does not respond or has relapsed after rituximab treatment. A third monoclonal antibody, currently in Phase 3 development, is ofatumumab (HuMax-CD20, Genmab and GlaxoSmithKline), which is being investigated for use in follicular lymphoma that no longer responds to rituximab.

Also at Phase 3 in NHL are enzastaurin (Lilly), which is given by mouth, bendamustine (Treanda, Cephalon), AMD3100 (Mozobil, Genzyme), which is designed to facilitate stem cell transplantation, and temsirolimus (Torisel, Wyeth), which is being studied in a different subtype of NHL called mantle cell lymphoma. Phase 2 development compounds include galiximab (Biogen Idec), mapatumumab (HGS-ETR1, Human Genome Sciences), and combinations of rituximab with bortezomib (Velcade, Millennium) or Interleukin-2 (Proleukin, Chiron).

The prospects for people with **multiple myeloma** have also improved with the authorisation of new treatments. Bortezomib (Velcade, Ortho Biotech), which belongs to a new class of agent called proteasome inhibitors, has been shown to lengthen the time before relapse and to extend survival (to 80 per cent survival at one year) in patients previously treated with chemotherapy, as compared with the previous standard treatment with high-dose dexamethasone (66 per cent one-year survival). Bortezomib is currently in Phase 3 study for first-line use in multiple myeloma. Also in Phase 3 study are lenalidomide (Revlimid, Celgene) and doxorubicin (Caelyx, Schering-Plough), which is indicated for use in advanced ovarian cancer and in AIDS-related Kaposi's sarcoma.

Several other new treatments for multiple myeloma have reached the Phase 2 stage, including XL999 (Exelixis), lestaurtinib (Cephalon), mapatumumab (Human Genome Sciences), and Aplidin (PharmaMar).

The longer-term future

Although recent advances in treating leukaemias and lymphomas may seem relatively modest, they are beginning to have a very real impact on survival prospects. Monoclonal antibodies offer new ways of working against malignant cells and generally have fewer disruptive side-effects than cytotoxic medicines. Given the large number of new compounds in the Phase 3 and Phase 2 pipeline, the outlook for improved and better-tolerated therapies for this diverse group of diseases is encouraging.

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M

MALARIA

What is malaria?

Malaria is a disease caused by one of four species of the parasite *Plasmodium*. It is spread by the bite of infected mosquitoes and is endemic in tropical and sub-tropical parts of the world (Figure 2). The *Plasmodium* parasite has a complicated life-cycle with several different stages, some found in the mosquito host and some in the liver and red blood cells of infected humans (Figure 1). Of the four *Plasmodium* species (*P. falciparum, P. vivax, P. ovale and P. malariae*), *P. falciparum* is the most dangerous and may cause coma, severe anaemia, kidney failure, convulsions and pulmonary oedema, in addition to a high fever. Untreated *P. falciparum* malaria has a high death rate. Fluctuating fevers, chills, malaise, nausea, muscle pains and headache are the most frequent symptoms of malaria, often accompanied by anaemia and jaundice, but may initially be mistaken for influenza. However, parasites can be seen in the blood through a microscope, confirming diagnosis.

Who does malaria affect?

The World Health Organisation has estimated that 300-500 million people worldwide are infected by malaria each year, and that the disease causes more than 1 million deaths a year. More than 85 per cent of these deaths are estimated to occur in Africa, and children under five years old account for the majority of cases. Malaria is not endemic in the UK, but approximately 2,000 cases occur every year in those returning from malaria-endemic countries. In 2005 there were 1,754 recorded cases in the UK (76 per cent of them due to *P. falciparum*) and 11 deaths.

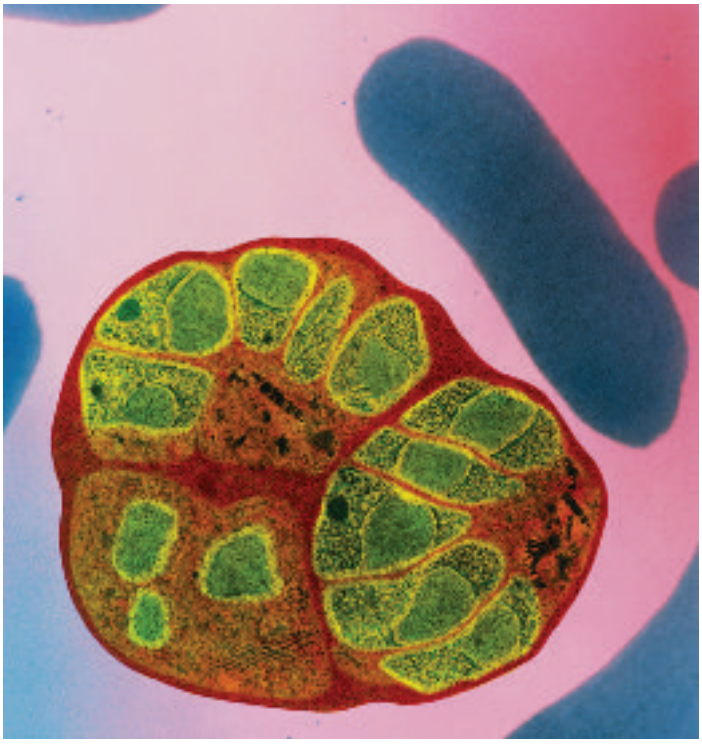

Figure 1: **Malaria parasites (merozoite stage, green) infecting a human red blood cell.**

Present treatments and shortcomings

Prophylaxis (prevention) is the most important consideration for travellers visiting areas where malaria is endemic, and a variety of physical measures are recommended (for example, use of impregnated mosquito nets, insect-repellent sprays, etc). However, preventive medicines are also necessary and several are available. Which one is chosen will depend on the types of malaria most often encountered in the area to be visited and their resistance to anti-malarial medicines. The parasite has become resistant to chloroquine (Avloclor, AstraZeneca) in many countries and other medicines will often be chosen, such as mefloquine (Lariam, Roche), doxycycline (Vibramycin-D, Pfizer) or atovaquone + proguanil (Malarone, GSK). The most common side-effects of these medications when used for prevention of malaria are gastrointestinal upsets (pain, nausea, vomiting, diarrhoea) and headache. Sensitivity to light may occur with doxycycline and dizziness or blurring of vision have been reported with chloroquine and mefloquine. Rarely, serious side-effects have been associated with mefloquine, such as seizures, mood changes or psychoses.

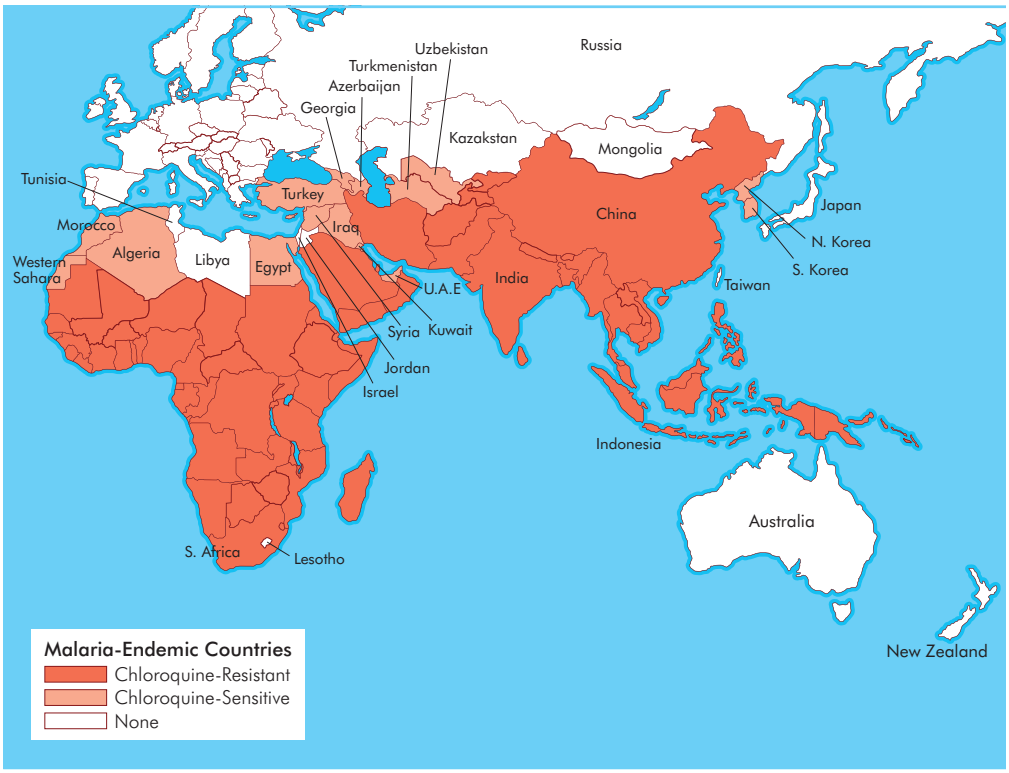

Figure 2: **Malaria is endemic in tropical and sub-tropical regions of Africa and Asia**
Source: Centers for Disease Control and Prevention

Treatment of malaria has in the past often been with quinine, and this may still be used in certain situations, but the WHO now recommends the use of combination therapies with two or more medications that act in different ways, in order to avoid the resistance which may develop if a single agent is used. In particular, combinations based on artemisinin and its derivatives (artesunate, artemether, artemotil, dihydroartemisinin) such as artemether + lumefantrine (Riamet, Novartis) are recommended. While low blood sugar levels are a common side-effect of quinine treatment, artemisinin derivatives are generally well tolerated.

What's in the development pipeline?

The growing problem of resistance means that development of new anti-malarial treatments is a continuing need. In addition, while current treatments are effective, they are generally too expensive for widespread use in the main malarial areas. Moreover, there is a pressing need for a preventive vaccine that could reduce the huge number of deaths caused by malaria in sub-Saharan Africa.

Several new malaria **treatments** are in development to counter the problem of resistance. At the Phase 3 stage, GlaxoSmithKline is developing a combination of chlorproguanil, dapsone and artesunate (CDA), while Sigma-Tau is studying a combination of dihydroartemisinin and piperaquine, an antimalarial medicine that has already been used successfully in China against resistant malaria. Pfizer has a combination of chloroquine and the antibiotic azithromycin also in Phase 3 trial.

New compounds in Phase 2 research include GSK's tafenoquine, an 8-aminoguinoline active against *P. vivax* malaria, Immtech's pafuramidine (DB 289), HE-2000 (Immunitin, Hollis-Eden) sanofi-aventis's ferroquine (SSR 97193), which has been shown to be active against chloroquine-resistant strains of *P. falciparum*, and RBx11160, from Ranbaxy. This last compound is intended as a replacement for artemisinin, which must be harvested from plants and which is consequently in limited supply. It will be used in combination with the long-acting compound piperaquine phosphate. Lastly, at Phase 1, Immtech has AQ13.

Figure 4: **Extracts from the plant *Artemisia annua* have been used for treating malaria since ancient times**

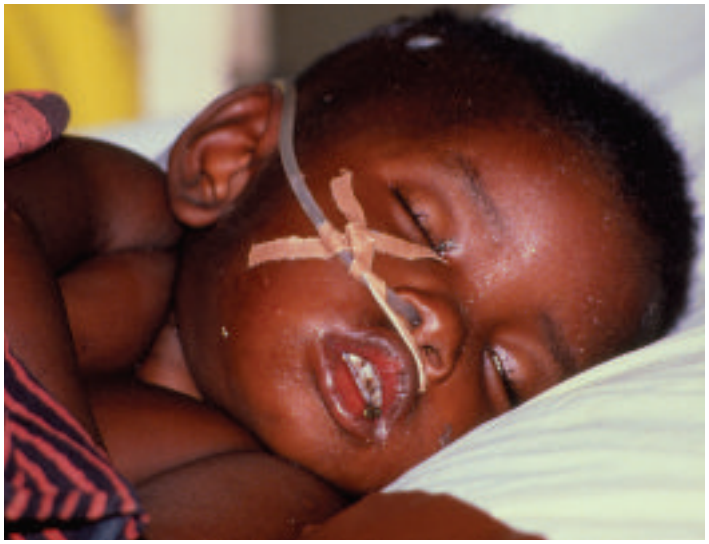

Figure 3: **A Tanzanian child receiving treatment for malaria. Children under 5 have a high risk of dying from malaria if untreated**

An effective **malaria vaccine** is the ultimate goal of research into prevention. This goal is still a long way from being achieved, but positive results have been reported in Phase 2 trials of a vaccine called RTS,S/AS02A (Mosquirix, GSK) directed against the stage of the malarial parasite that is injected when a mosquito bites. In an 18-month follow-up of children in Mozambique who had been given three doses of the vaccine, there was a 35 per cent reduction in malaria episodes.

Other companies are also developing vaccines that act against various stages of the disease. Pevion Biotech has a vaccine (PEV3A) in Phase 2 trial and Oxxon Therapeutics is collaborating with the Malaria Vaccine Initiative and the Wellcome Trust on two vaccine projects. In addition, Crucell has a malaria vaccine based that is about to start Phase 1 trials. Vaccines directed against the blood-borne stages of the disease have also been extensively researched, but none has yet shown sufficient protective efficacy to merit full development.

All of the vaccines mentioned above are directed against the *P. falciparum* form of malaria, which is the most widespread and difficult to treat, but the Malaria Vaccine Development Branch of the National Institutes of Health in the United States has carried out Phase 1 studies on a vaccine (Pvs25H) against *P. vivax* malaria, which is the next most common form.

MIGRAINE

What is migraine?

Migraine is a severe form of headache which can last from a few hours to 72 hours or longer. Symptoms are very variable, but five stages are recognised:

- the *prodrome*, when there may be mood variations, neck stiffness and changes in gut activity
- the *aura* - a short period of visual or sensory disturbances such as patterns of flickering lights
- *severe headache*, aggravated by light and sound, that may be accompanied by nausea or vomiting
- *resolution*, as the headache declines, and deep sleep may occur
- the *postdrome*, when the patient feels fatigued and lethargic.

Between two main forms of migraine are recognised: those with and those without aura. 10-30 per cent of people with migraine experience migraine with aura (also known as classical migraine).

A wide range of factors can precipitate an attack, such as certain foods, menstruation, disturbed sleep pattern, stress, and smoking. There have been many theories proposed to provide an explanation for how migraine arises, mostly involving some aspect of blood flow or brain activity.

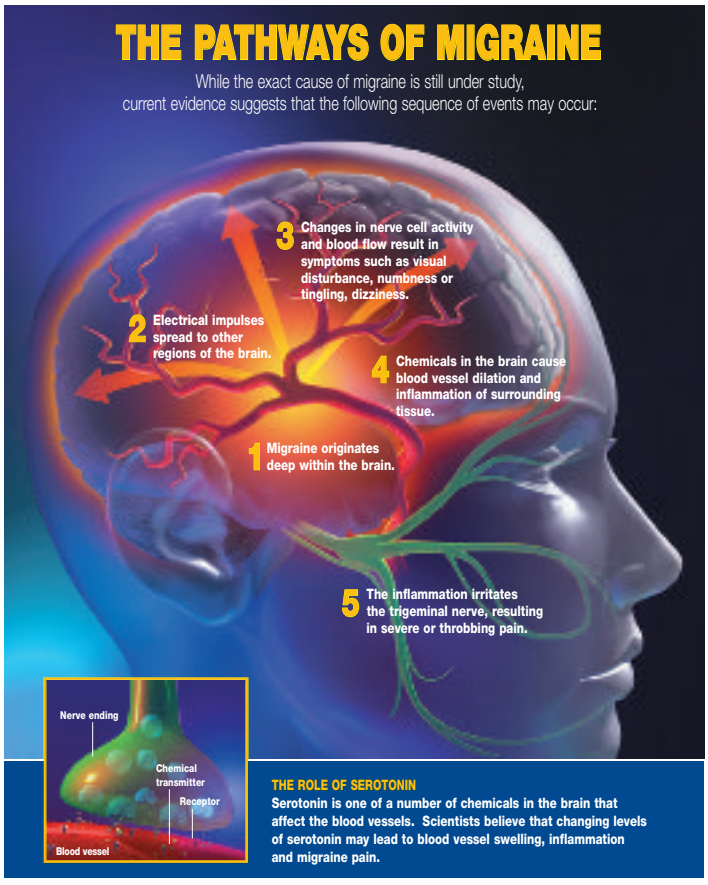

Figure 1: **The pathways of migraine**

NEW SINCE 2000

2001 - Zolmitriptan orodispersible tablets (Zomig Rapimelt, AstraZeneca)

2002 - Frovatriptan (Migard, Menarini)

2005 - Topiramate (Topamax, Janssen-Cilag)

Who does migraine affect and what does it cost?

Migraine headaches are thought to affect almost six million people in the UK, with more than twice as many women affected as men. Many migraine sufferers treat themselves with over-the-counter pain medications such as aspirin, so that in these cases the cost does not fall on the NHS. Migraine has been estimated to cause the loss of 25 million days of work/education per year in the UK.

Present treatments and shortcomings

Many products are available for migraine, some for prevention (prophylaxis) and others to treat an attack. Prophylactic agents include **Beta-blockers** (metoprolol, from AstraZeneca/Novartis, or propranolol, nadolol, timolol, from AstraZeneca, sanofi-aventis and Valeant respectively), **5HT-antagonists** such as pizotifen and methysergide (Novartis), Merck Sharp & Dohme's cyproheptadine, and the **central alpha-agonist** clonidine (Boehringer-Ingelheim). More recently, the anti-epileptic medication topiramate (Topamax, Janssen-Cilag) has also been made available for the prevention of migraine. Though useful, some of these prophylactic agents have side effects such as sedation, abdominal cramps, nausea, dizziness and so on.

Therapy for an acute attack most often involves painkillers for mild to moderate attacks, or ergotamine for more severe attacks, perhaps combined with an anti-emetic for feelings of nausea. However, in recent years, selective serotonin receptor agonists, known as 'triptans' have been introduced and have quickly taken a leading position in migraine therapy. The first of these, sumatriptan (Imigran, GlaxoSmithKline) was originally given by injection, but is now available in oral and nasal spray forms . Other triptans available in the UK are almotriptan (Almogran, Organon), naratriptan (Naramig, GSK), zolmitriptan (Zomig, AstraZeneca), rizatriptan (Maxalt, Merck Sharp & Dohme), eletriptan (Relpax, Pfizer) and frovatriptan (Migard, Menarini). Non-tablet forms of zolmitriptan and rizatriptan that dissolve rapidly in the mouth without water are also available and zolmitriptan is also available as a nasal spray. Frovatriptan has a longer duration of action than other triptans. The triptans are thought to act by shrinking dilated blood vessels in the brain, but may also constrict the coronary arteries and are therefore not suitable for people with high blood pressure, coronary heart disease or kidney or liver problems.

What's in the development pipeline?

Although some further development of triptans is still going on, such as Merck Sharp & Dohme's studies of rizatriptan in menstrual migraine and for the treatment of migraine-associated nausea, new medicines in development mainly act in different ways from triptans.

Migraine prophylaxis

Several companies are conducting trials in the prevention of migraine with medicines that have already been indicated for other uses. Takeda has ramelteon in trial for the prevention of migraine and Allergan is studying botulinum toxin (Botox) for this purpose. At Phase 2, Lilly is trialling olanzapine (Zyprexa; indicated in the UK for treating schizophrenia and mania in bipolar disorder) and Eisai is studying the anti-convulsant E-2007. Also new is tonabersat (Minster Pharmaceuticals), which has started Phase 2 trials for the prevention of migraine with and without aura.

Migraine treatment

A neuropeptide called calcitonin gene-related peptide (CGRP) found in the brain is believed to play a key role in migraine. Boehringer-Ingelheim is conducting Phase 2 trials of BIBN 4096BS (olcegepant), a selective CGRP antagonist that has already been reported in preliminary trials to show evidence of activity in counteracting acute pain and decreasing headache recurrence. Other agents for acute migraine treatment in Phase 2 trial include GlaxoSmithKline's GSK 274150, MK-0974 (Merck Sharp & Dohme), a glutamate receptor antagonist from Eli Lilly and a metered-dose inhaler compound (Marinol; Solvay/Nektar).

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MULTIPLE SCLEROSIS

What is multiple sclerosis?

Multiple sclerosis is a disorder of the central nervous system in which nerve cells lose their insulating sheath, called myelin. Nerves are able to regenerate their myelin sheath, but its destruction in MS is so rapid that the nerve may die before regeneration can occur. This results in the appearance of plaques *(sclera)* in the brain and spinal cord, in which nerve cells are replaced by fibrous connective tissue. Clinical symptoms depend on the location of the damage, but can include vision loss or double vision, speech difficulties, muscular weakness, abnormal skin sensations, bladder problems, fatigue, pain and mood alterations. Multiple sclerosis typically shows periods of acute illness (*exacerbations*) and remissions, although there is often a general worsening over time. Magnetic resonance imaging (MRI) is a sensitive diagnostic technique that can be used to measure its progress.

The cause of multiple sclerosis is unknown and its progress cannot be predicted with certainty. No infectious agent has been definitely linked to MS, but the immune system is thought to be involved in the inflammation that accompanies myelin destruction. Two distinct patterns of MS are generally recognised. At diagnosis, about 15 per cent of those affected have *primary chronic progressive* MS (CP-MS) and 85 per cent have *relapsing-remitting* MS (RR-MS). Over time, about half of the RR-MS patients develop *a secondary progressive* form (SP-MS). In relapsing-remitting MS, problems with the nervous system appear suddenly, followed by slow improvement. About 15-20 per cent of these patients relapse within the first year: the shorter the time to relapse, the poorer the prognosis. In CP-MS, the deterioration is gradual and the intervals of remitted disease are absent.

Who does MS affect and what does it cost?

MS is estimated to affect around 85,000 people in the United Kingdom and typically strikes young adults in their 20s and 30s. It is more common in women than in men by a ratio of 3:2. A recent study of treatment costs in nine European countries estimated that the total average annual cost per patient was £12,300 for someone with mild disease, almost £25,000 for moderate disease and as much as £42,300 for those with severe disease.

Present treatments and shortcomings

Acute exacerbations of MS are usually treated with anti-inflammatory steroids, such as prednisone, methylprednisolone and dexamethasone. These reduce the duration and severity of acute attacks but do not alter the condition's long-term course. Their possible adverse effects (skin reactions, weight gain, osteoporosis, mood alterations) make them unsuitable for prolonged use. In addition, baclofen, tizanidine or benzodiazepines may be given to relax muscular spasms and anticholinergic drugs (oxybutinin, tolterodine, propiverine) can be helpful to treat urinary complications.

Newer treatments for RR-MS include three forms of recombinant beta interferon. These are interferon beta-1b from Schering (Betaferon), interferon beta-1a (Avonex) from Biogen Idec and Serono's interferon beta-1a (Rebif). All are given by injection. These reduce the frequency of relapses in RR-MS by about 30 per cent as well as the severity of attacks, although not everyone responds to them. They are, however, not a cure for the disease and may cause flu-like symptoms in some people. Moreover, neutralising antibodies may develop in some cases, potentially reducing their effectiveness.

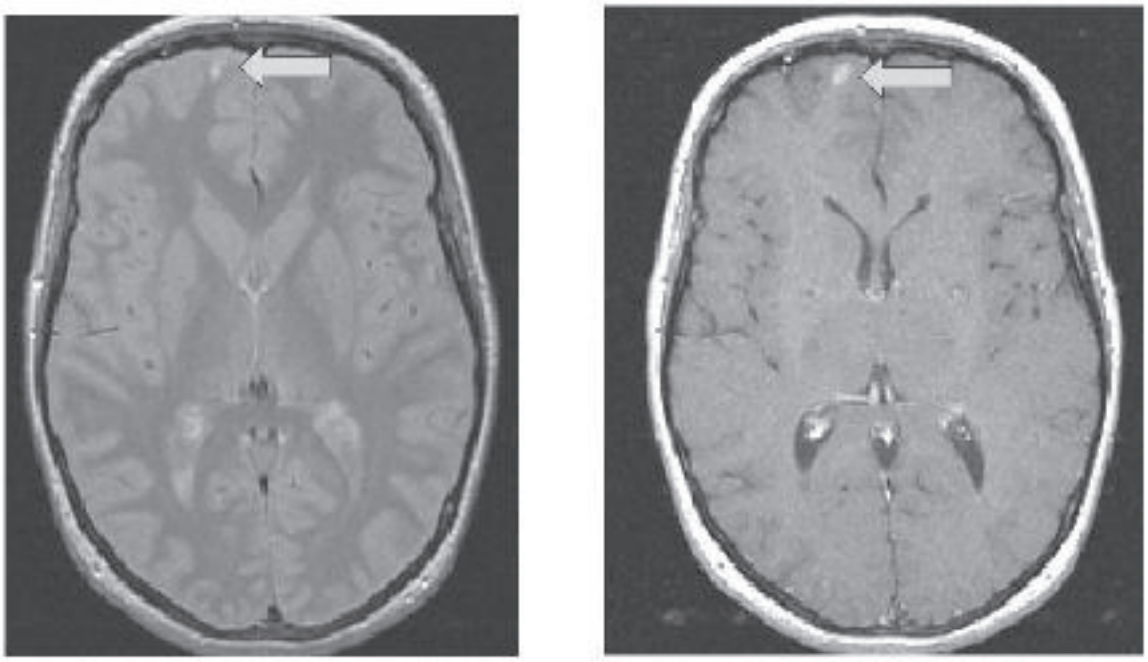

Figure 1: **Scanned image of a 37-year old woman with acute left optic neuritis, several paraventricular lesions and one acute Gadolinium (Gd)-enhancing subcortical lesion (see right sided figure). The Gd-enhancement implies acute or active inflammation and indicates blood-brain-barrier breakdown.**
(Courtesy of the Institute of Neurology)

Glatiramer acetate (Copaxone, Teva), another treatment for RR-MS, is believed to work in a quite different way from beta interferon. It is thought to mimic the protein component of the nerve's myelin sheath and act as a decoy during acute attacks by immune system cells (T-cells) which would otherwise damage myelin. It reduces the frequency and severity of relapses to a similar extent to beta interferon and is given by daily injection. Ten-year study data show that long-term use of glatiramer can reduce the relapse rate by as much as 80 per cent. Adverse reactions may include redness and pain at the injection site, flushing, chest pain, muscle weakness and nausea.

The most recently introduced medication for RR-MS is natalizumab (Tysabri, Biogen Idec), for use in those with very active RR-MS or those who have not responded to treatment with beta-interferon. Natalizumab is given by intravenous infusion every four weeks and, because its use has been associated with an increased risk of a potentially fatal opportunistic viral infection of the brain, it may not be used in those at increased risk for such infections, including people undergoing immunosuppressive treatment. It may also not be given in combination with beta-interferon or glatiramer acetate. In clinical trials, natalizumab has been shown to be highly effective in reducing disability progression, the rate of relapses and the number of new or enlarging brain lesions detected by MRI. Persistent antibodies against natalizumab developed in about 6 per cent of those exposed to it and may potentially limit its effectiveness.

What's in the development pipeline?

Compounds are in development for all types of MS. Until now, no medication has been indicated for the **primary progressive** form of MS, but the monoclonal antibody rituximab (Mabthera, Roche), already available for use in non-Hodgkin's lymphoma and rheumatoid arthritis, is now in Phase 2/3 trial for this category of MS, as well as being in Phase 2 trial for the relapsing-remitting form. **Secondary progressive** MS is also being studied; BioMS Medical is conducting a Phase 2/3 trial in Canada, the UK and Scandinavia with MBP8298, which is given intravenously every six months, to demonstrate delay of progression in this form of the disease. In an earlier Phase 2 study, some patients treated with MBP8298 had a median time to disease progression of 78 months, as compared with 18 months for those given placebo.

Trials are also in progress in seeking new medicines for some of the troublesome symptoms of MS. GW Pharmaceuticals has conducted Phase 3 studies of the ability of the cannabis-based Sativex (taken as a spray in the mouth) to relieve involuntary muscular contractions and is planning to start trials in pain associated with MS. Also, Avanir Pharmaceuticals is conducting a Phase 3 trial of AVP 923 in involuntary emotional expression disorder.

Most research is, however, focused on the **relapsing-remitting** form of MS. At the Phase 3 stage, Novartis is conducting a trial of the oral compound fingolimod (FTY720), which lowers the number of circulating activated T-cells and has demonstrated a reduction in relapse rate in earlier trials, Serono has cladribine under study, Biogen-Idec has BG-12 and sanofi-aventis is investigating the immunomodulator teriflunomide.

Many compounds are being studied in Phase 2 trials. Abbott has ABT-874 and Biogen Idec is studying the orally active compound CDP323 and the monoclonal antibody daclizumab, which is already available for the prevention of organ rejection in kidney transplantation. Other monoclonal antibodies in trial are alemtuzumab (Mabcampath, Schering), already available for use in chronic lymphocytic leukaemia, and MLN1202, from Millennium Pharmaceuticals. Other agents at this stage include Eisai's E-2007, GSK's GSK 683699, and Medicinova's Ibudilast. The antidiabetic agent pioglitazone (Takeda) is also being evaluated in MS, because of its anti-inflammatory properties.

The longer-term future

More than 25 new compounds are currently in clinical trials for MS and it is not possible to discuss all of them here. There is, however, reason to hope that future therapy for this devastating disease may be more than just palliative and that it may be possible to delay substantially, or even halt, progression of multiple sclerosis.

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OBESITY

What is obesity?

Obesity is described as an excessive amount of body fat, rather than just excessive weight, and is a potentially serious health problem. Some people are obese because of an underlying medical condition, many more because their calorific intake is too great - a behavioural, rather than a medical, problem. A person is considered to be obese when their body mass index (BMI, defined as body weight in kilograms divided by the square of the person's height in metres) exceeds 30. Such people have a markedly higher chance of death compared with others of the same age and normal weight, owing to the link between obesity and diabetes, high blood pressure, atherosclerosis, gall bladder disease and some cancers.

Who does obesity affect and what does it cost?

Overweight and obesity are a problem affecting a large proportion of the population, regardless of age and social status. In 2003, 65 per cent of men and 55 per cent of women in England had a BMI above 25, and approximately one quarter of all children aged 11-15 were obese.

The total cost to the NHS of treating obesity and its consequences is estimated at £1 billion a year and the wider costs to the community at a further £2.3-2.6 billion a year.

Present treatments and shortcomings

Three medications are currently available for the treatment of obesity. All are used in conjunction with diet and exercise modification. One is orlistat (Xenical, Roche) which acts within the stomach and small intestine to prevent breakdown and absorption of dietary fats. In clinical trials, 20 per cent of patients taking orlistat lost 10 per cent or more of their body weight over two years, compared with 8 per cent of patients taking placebo.

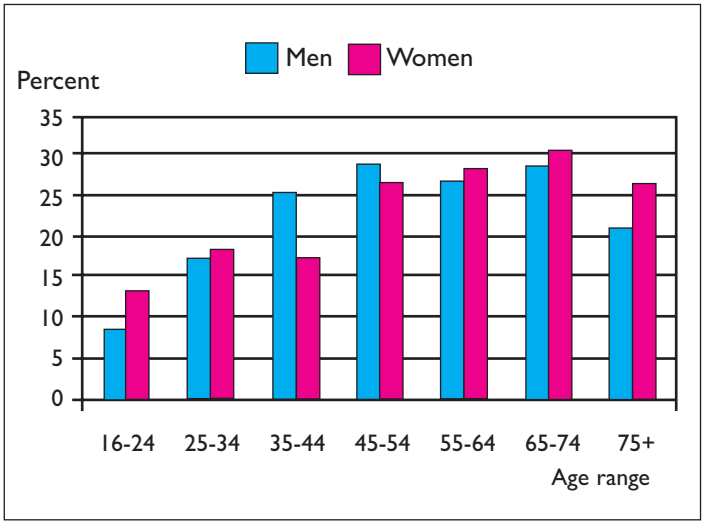

Figure 2: **The proportion of obese (BMI ≥30) men and women in England increases with age.**
Source: Health Survey for England, 2003.

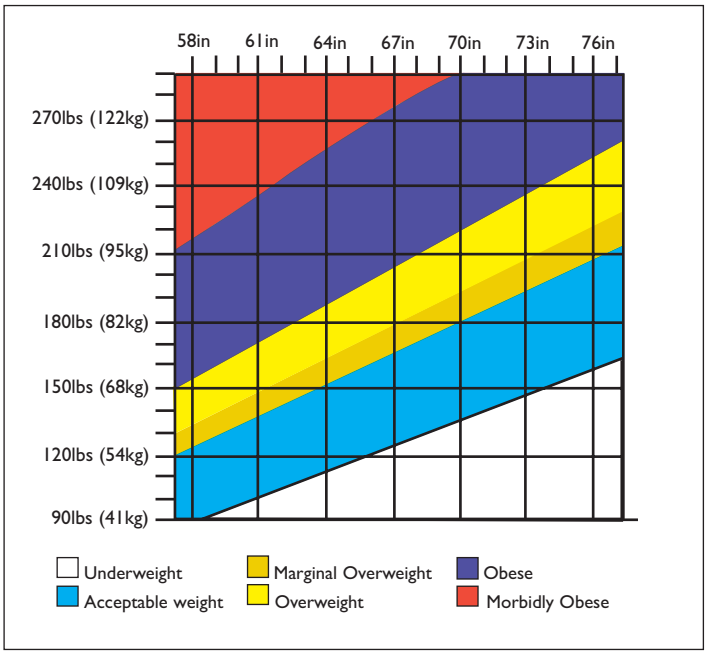

Figure 1: **Acceptable weight for women, based on height and Body Mass Index. A person with a BMI of 25-30 is considered to be overweight; a BMI over 30 indicates obesity. A BMI of 20-25 is considered the acceptable weight range for good health.**

The increased fat content of the stool can, however, lead to gastrointestinal problems such as flatulence and faecal incontinence.

The second is sibutramine (Reductil, Abbott), which is a serotonin and noradrenaline reuptake inhibitor. Sibutramine enhances feelings of fullness and increases the rate at which the body burns food. Headache, dry mouth, dizziness and constipation are the most common adverse effects. Rapid heartbeat and raised blood pressure are observed less frequently.

The third medication is rimonabant (Acomplia, sanofi-aventis). It is used in obese people and those with BMI greater than 27 who have dyslipidaemia or type 2 diabetes. The most common side effects observed are nausea, mood alteration with depression or anxiety and dizziness.

What's in the development pipeline?

Several cannabinoid inhibitors are in development. At Phase 3, Pfizer is investigating CP-945,598 and Merck Sharp & Dohme is studying MK-0364. Sanofi-aventis has a follow-up compound to rimonabant (AVE 1625) in Phase 2 trial, while Bristol-Myers Squibb and Solvay are collaborating on SLV 319 (also Phase 2). Compounds interacting with this receptor system in preclinical research include GRC 10389 (Glenmark), V24343 (Vernalis) and E-6776 (Lab. Dr Esteve).

Two lipase inhibitors are currently in clinical trial. Alizyme has cetilistat, which has completed two Phase 2 trials. In these trials, cetilistat demonstrated a similar short-term (12 week) weight loss to orlistat, but was associated with a lower level of gastrointestinal side-effects. The other compound in development in this class is GT 389-255 (Peptimmune), which is in Phase 1 trials.

Increasing energy expenditure would seem to be a way of promoting weight loss, and sibutramine has long been known to increase metabolism. A compound which does this is in Phase 2 trial: Kyorin's KRP-204. A different compound that affects fat metabolism is AOD-9604, which is being developed by Metabolic Pharmaceuticals, and is currently in Phase 2 trial.

Other approaches being explored are those that seek to reduce appetite and food intake. These may act either centrally (in the brain) or elsewhere. Centrally-acting agents include APD-356 (Lorcaserin, Arena Pharmaceuticals) at Phase 3 and NS 2330 (tesofensine, NeuroSearch), the appetite suppressant S-2367 (Shionogi), and TM30338 (7TM Pharmaceuticals) all at Phase 2, while PRX-07034 (EPIX Pharmaceuticals), is in Phase 1 trials. Other compounds under development that affect appetite include three based on naturally-occurring substances: pramlintide (Amylin), which induces feelings of fullness after eating (Phase 2), the injectable AC-162352 (Amylin) and a nasal spray form of PYY3-36 (Nastech), both at Phase 1.

In addition, several companies have other compounds in development, including Merck Sharp & Dohme (MK-0493, at Phase 2), Pfizer (CP-741,952, also at Phase 2), GSK (869682, Phase 2 and 189075, Phase 1), Eli Lilly (five candidates due to enter Phase 1) and AstraZeneca (AZD 1175 and AZD 2207, both at Phase 1). With such a range of potential new medicines under investigation, clinicians can expect to have a wider range of treatments for the growing problem of obesity, with the potential to prevent many future cases of obesity-related diseases.

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OSTEOARTHRITIS

What is osteoarthritis?

Osteoarthritis is the collective name for a family of bone diseases involving the degeneration of cartilage and abnormal growth of new bone and connective tissue. In late stage cases, abnormal bone growth causes visible bumps and ridges around the joints. Osteoarthritis can affect most joints, including the spine, but is more common in the knees, hips, feet and hands. Nodal osteoarthritis, affecting the finger joints, which occurs predominantly in middle-aged women, is clinically distinct from, for example, osteoarthritis of the knees, which is often related to obesity and shows a more even sex distribution. Symptoms depend on the joints affected, but include pain, stiffness and loss of function. Pain can become severe in the later stages of osteoarthritis, when replacement of the joint affected may be necessary. In 2005, there were 62,677 hip replacements and 62,818 knee replacements carried out in England and Wales.

Who does osteoarthritis affect and what does it cost?

By the age of 65, 80 per cent of people show evidence of osteoarthritis in X-rays, although only about 25 per cent have symptoms. Estimates have put the number of people suffering from osteoarthritis in the United Kingdom at 8.5 million, with more than 2 million visiting their GP each year because of osteoarthritis. The prevalence of osteoarthritis increases markedly with age in both men and women.

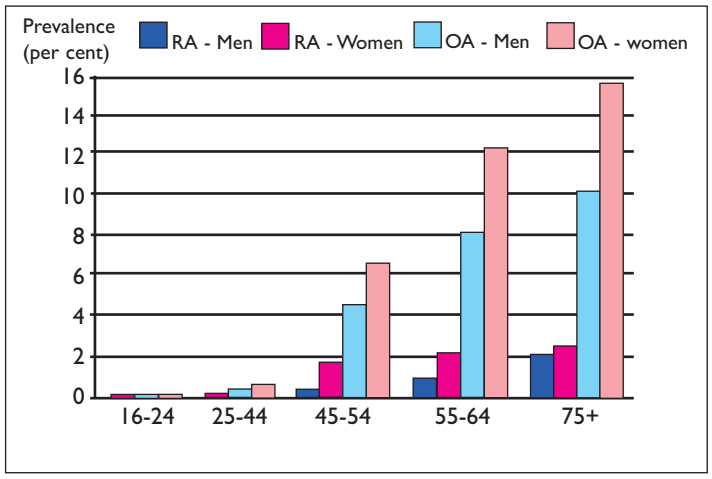

Figure 1: **Prevalence of rheumatoid arthritis (RA) and osteoarthritis (OA) by age and sex.**
Source: Arthritis: The Big Picture, Arthritis Research Campaign, 2002.

The total cost of arthritis (of which osteoarthritis makes up the largest component) to the NHS and social services has been estimated at £5.5 billion in 2000. Of this, the cost of operations to replace hip and knee joints was £405 million, other hospital costs were £259 million, GP consultations cost £307 million, and the cost of medications was £341 million. In addition, 206 million working days were lost in that year due to arthritis, corresponding to a loss of production of over £18 billion.

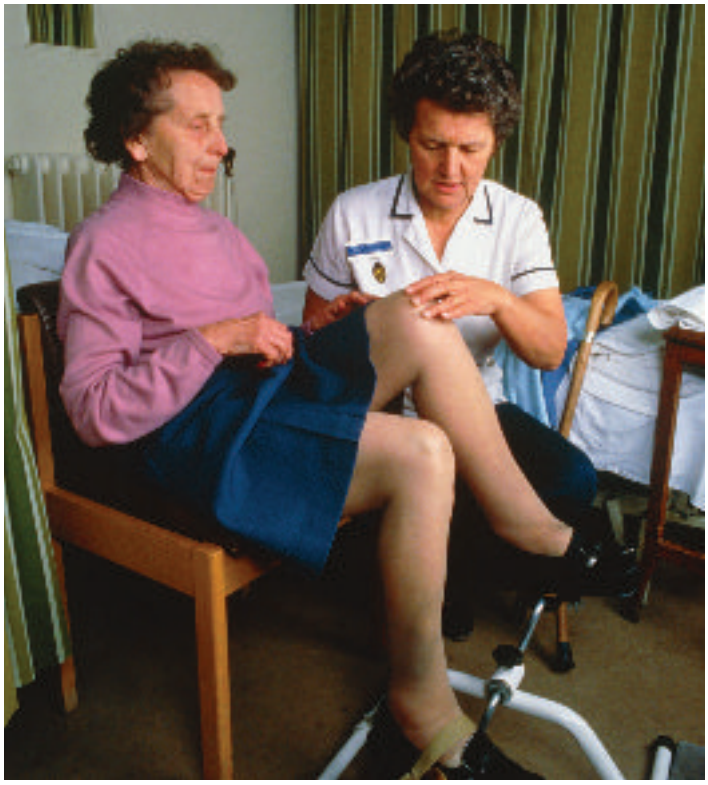

Figure 2: **Physiotherapy helps to mobilise joints affected by osteoarthritis**

Present treatments and shortcomings

Current treatments for osteoarthritis are solely concerned with managing symptoms such as pain; there is no medication that has been proven to prevent the disease or modify its course. Exercises to build muscle are useful in people who are still active, simple painkillers or non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed for pain control, and corticosteroid injections into the joint can help in acute cases. In addition, various preparations are available for injection into the knee joint to improve the condition of the joints, but this does not alter the course of disease.

NSAIDs inhibit an enzyme called cyclo-oxygenase (COX), blocking the formation of inflammatory prostaglandins. COX exists in two forms: COX-1 and COX-2. Prostaglandins produced by COX-2 are inflammatory and damage the gut, leading to gastric ulcers and bleeding, but those from COX-1 have a protective effect. Of the older NSAIDs, some inhibit COX-2 more than COX-1 but are not entirely selective. Two of these are meloxicam (Mobic, Boehringer Ingelheim) and nabumetone (Relifex, Meda). Both have a lower risk of ulcers than NSAIDS that mainly inhibit COX-1, such as indomethacin, sulindac, aspirin and piroxicam.

COX-2 selective NSAIDs have been developed and introduced, but some have had to be withdrawn, following the finding of a raised incidence of heart problems. There is evidence that the risk of such side-effects differs from one selective COX-2 inhibitor to another

and three remain available for pain relief in osteoarthritis. These are: celecoxib (Celebrex, Pfizer), etoricoxib (Arcoxia, Merck Sharp & Dohme), and lumiracoxib (Prexige, Novartis). Some of the older and widely used NSAIDs, ibuprofen and diclofenac, have also been associated with heart problems. While the risk of such side-effects remains small in all of these cases, the physician and patient must make any decision on the long-term use of high doses of painkillers on the basis of weighing up both risks and benefits.

What's in the development pipeline?

Additional pain-killers, including selective inhibitors of COX-2, are being studied for use in osteoarthritis and Daiichi-Sankyo has CS-706 in Phase 2 trial. NicOx is developing a version of naproxen (HCT 3012, naproxcinod), which has reached Phase 3 trial in osteoarthritis of the knee. This compound is expected not to show the blood pressure-raising effect of NSAIDs that may be responsible for the increased risk of heart problems. Pfizer also has a compound (CJ-23423) in phase 2 trial for osteoarthritis. Meanwhile, CombinatoRx Inc has reported positive results with a Phase 2 study of its CRx-102 for pain reduction in osteoarthritis of the hand.

New treatment approaches are also being studied by various companies. Sanofi-aventis has HOE 140 (icatibant) in Phase 2 trial and an oral form of calcitonin (SMC 021) being studied by Novartis and an anti-inflammatory compound (SC-84250) from Pfizer have reached the same stage. At Phase 1, Schwarz Pharma (UCB) is developing lacosamide and Wyeth (AGG-523, PLA-695) and Merck Sharp & Dohme (MK0822) also have compounds in development.

The possibility of modifying disease progress is also being investigated. Risedronate (Actonel, Procter & Gamble), a compound in the bisphosphonate group, slows bone destruction in osteoporosis and, as tiny fractures of bone at the joint surface have been suggested as a possible underlying cause of osteoarthritis, it might slow disease progress in osteoarthritis too. Although a reduction in pain was not found, risedronate did reduce the level of a marker of bone turnover that is associated with the progression of osteoarthritis. Also, GlaxoSmithKline is investigating an inhibitor (GSK 462795, relacatib) of an enzyme that may affect bone destruction, and this is at Phase 1.

NEW SINCE 2000

2000 - Celecoxib (Celebrex, Pfizer)

2002 - Etoricoxib (Arcoxia, Merck Sharp & Dohme)

2005 - Lumiracoxib (Prexige, Novartis)

FOR FURTHER INFORMATION CONTACT:

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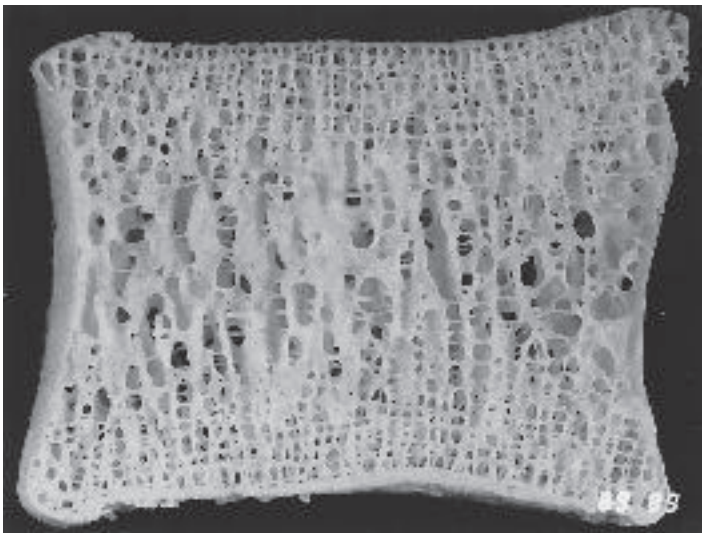
OSTEOPOROSIS

What is osteoporosis?

Osteoporosis is a condition affecting the body's bones, in which there is an imbalance between bone formation and bone resorption (the breakdown and assimilation of bones by the body), leading to excessive loss of bone (Figure 1). The weakened bones are eventually unable to support even normal activities and fractures occur, especially in the hip, wrist and vertebrae, leading to substantial pain and incapacity. Osteoporosis is an insidious disease, as the affected individual feels well and is often unaware that bone loss is taking place until a fracture occurs.



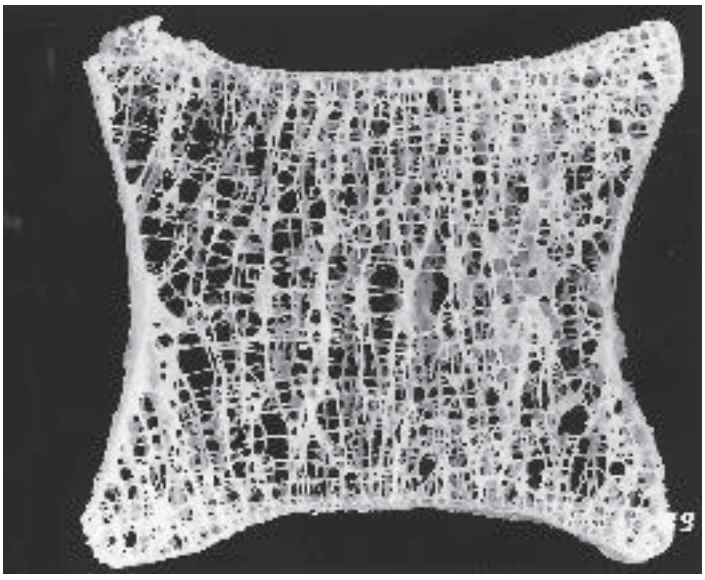


Figure 1: **A normal compared with an osteoporotic spinal vertebra.** (Courtesy of Professor Alan Boyde of University College, London)

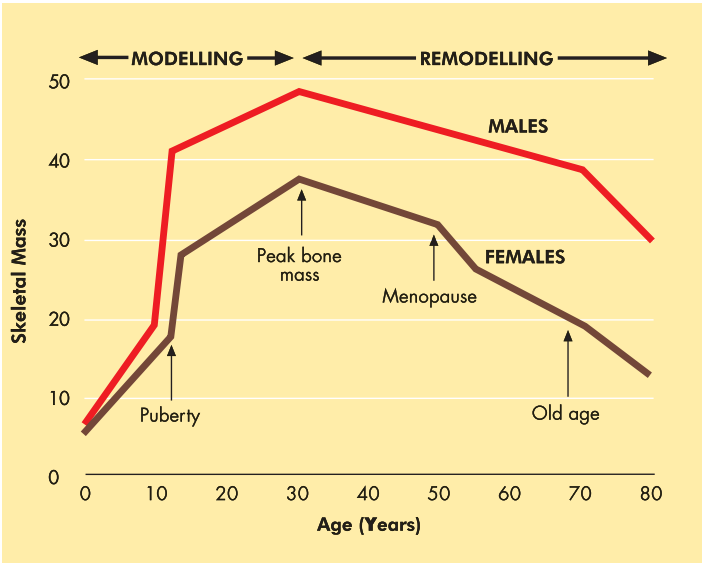


Figure 2 **Schematic diagram of bone mineral density throughout life**

Bone is constantly being renewed (remodelling) from birth to death (Figures 2 and 4). Many factors influence the maximum bone mineral density (BMD) reached and the rate of subsequent decline, including genetic makeup, race, physical activity, nutrition and exercise (especially in childhood), and vitamin D intake. Bone remodelling is under hormonal control and the drop in level of the sex hormone oestrogen in women after the menopause greatly accelerates bone loss. Osteoporosis may also develop as a result of high-dose or prolonged treatment with corticosteroids or, less commonly, some other medications, or in association with certain inflammatory, gastrointestinal or endocrine diseases.

Who does osteoporosis affect and what does it cost?

The National Osteoporosis Society has estimated that as many as 3 million people in the UK are affected by osteoporosis. The disease causes over 60,000 hip fractures, 50,000 wrist fractures and 120,000 spinal fractures each year. One woman in two and one man in five will suffer a fracture after the age of 50. The cost of treating hip fractures alone, including long-term nursing care, is estimated at £1.73 billion a year in the UK, with a recent study putting direct NHS costs at over £12,000 per case.

Present treatments and shortcomings

A wide range of hormone replacement therapy (HRT) treatments are available for managing the symptoms that arise from the fall in oestrogen level at menopause. HRT is also recognised to improve bone mineral density and reduce the risk of hip and spinal fractures. It has, however, become clear that HRT treatments may increase the risk of venous thromboembolism (see *Thrombosis*) and stroke, and may slightly increase the risk of breast cancer. Current medical thinking suggests that HRT use should be restricted to relief of menopausal symptoms, at the lowest effective dose, and not used long-term to protect against osteoporosis.

Raloxifene (Evista, Lilly), a selective oestrogen receptor modulator (SERM), has been introduced for the prevention and treatment of

post-menopausal osteoporosis. It increases BMD and reduces the rate of vertebral (but not hip) fractures. It has been shown to have a favourable effect on blood lipid levels, but does not act on the uterus (unlike oestrogen) and so can be used safely in women who have not had a hysterectomy. It does not increase the risk of breast cancer, unlike the oestrogen in HRT, but there is still an increased risk of venous embolism. There was an increased incidence of hot flushes during the first six months of treatment in clinical trials.

The main agents used for the treatment of osteoporosis are the bisphosphonates. They act by binding to bone, where they stop cells called osteoclasts, which are involved in breaking down bone, from digesting the bony tissue (Figure 4) and thus lower the risk of fracture. Those currently available in the UK are etidronate (Didronel PMO, Procter & Gamble), alendronate (Fosamax, Merck Sharp & Dohme) and risedronate (Actonel, Procter & Gamble). Alendronate and risedronate are also available for the prevention of post-menopausal osteoporosis. Their main disadvantages are that they are not readily absorbed in the gut and have a tendency to irritate the oesophagus. All are available in oral tablet form for osteoporosis treatment (usually taken daily or once a week).

Strontium ranelate (Protelos, Servier) is an oral agent for treating osteoporosis which is effective in preventing both vertebral and hip fractures. It has a dual action, both increasing bone formation and reducing bone resorption and is effective in increasing BMD. The main side-effects observed in trials were headaches, diarrhoea and nausea. It should be used with caution in patients at raised risk of venous thromboembolism.

Teriparatide (Forsteo, Lilly) is a treatment for osteoporosis that also works in a different way. It stimulates bone formation by increasing the number and/or activity of bone-forming cells called osteoblasts (Figure 4). It is administered once daily by injection for a maximum of 18 months. Teriparatide has been shown to reduce the rate of new vertebral (but not hip) fractures in post-menopausal women by more than 50 per cent.

NEW SINCE 2000

2000 - Alendronate (Fosamax, Merck Sharp & Dohme)

2001 - Calcitonin (Micalcic, Novartis) nasal spray form

2003 - Risedronate (Actonel, P&G) once-a-week form

2003 - Teriparatide (Forsteo, Lilly)

2004 - Strontium ranelate (Protelos, Servier)

2005 - Ibandronate, oral (Bonviva, Roche)

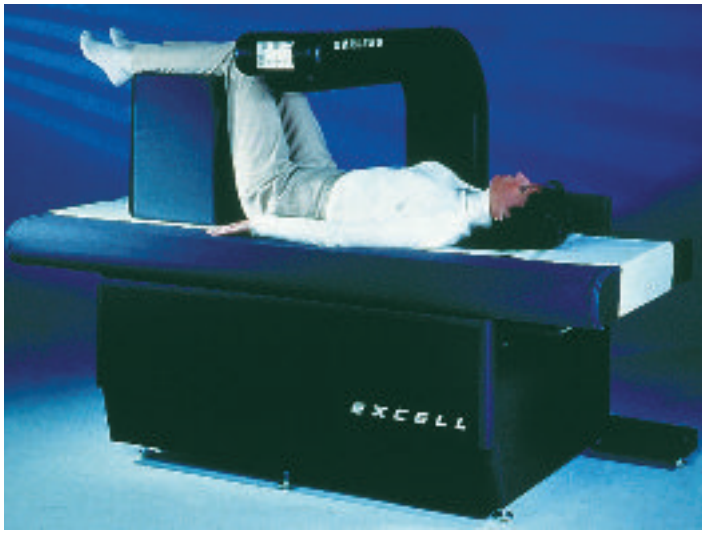


Figure 3 **A modern scanner used for bone mineral density measurements. BMD is the best predictor of fracture risk.** (Courtesy of Norland Medical Systems Inc)

Other medicines for OP include calcitriol (Rocaltrol, Roche) and combinations of calcium salts and vitamin D3 (usually given in addition to other medicines such as bisphosphonates), such as Procter & Gamble's Cacit D3 and Calcichew D3 Forte from Shire. Synthetic salmon calcitonin (a naturally occurring hormone) also prevents bone resorption. It is available from Novartis (Miacalcic) as a nasal spray, but is mainly used in patients for whom HRT and bisphosphonates are unsuitable.

What's in the development pipeline?

Preotact, developed by NPS Pharmaceuticals and Nycomed, is an injectable preparation of human **parathyroid hormone** that has been shown to reduce the risk of new vertebral fractures in women with or without pre-existing fractures resulting from osteoporosis. Other related preparations are in earlier phases, including a nasal spray (CHS13340, Chugai, at Phase 2), an oral compound in Phase 1 trial (768974, GSK/Unigene) and BA058 (Radius), which is also in Phase 1.

Three new **selective oestrogen receptor modulators** are in Phase 3 trial and are potential alternatives to raloxifene. Lasofoxifene (Oporia, Pfizer) has been shown to be effective in increasing lumbar spine BMD. Bazedoxifene (Viviant, Wyeth) has also been studied for its ability to reduce the incidence of new vertebral fractures in postmenopausal osteoporosis. Wyeth also has a Phase 3 trial in progress in which bazedoxifene is given together with oestrogen for prevention of osteoporosis. Meanwhile, arzoxifene (LY353381, Lilly) is also in Phase 3 trial for vertebral fracture reduction.

An additional **bisphosphonate** is also in Phase 3 trial. Zoledronate (Zometa, Novartis) is already available for treating raised levels of calcium in the blood in cancer and a trial is examining its ability to prevent new hip and vertebral fractures in osteoporosis. This bisphosphonate is given by injection only once a year.

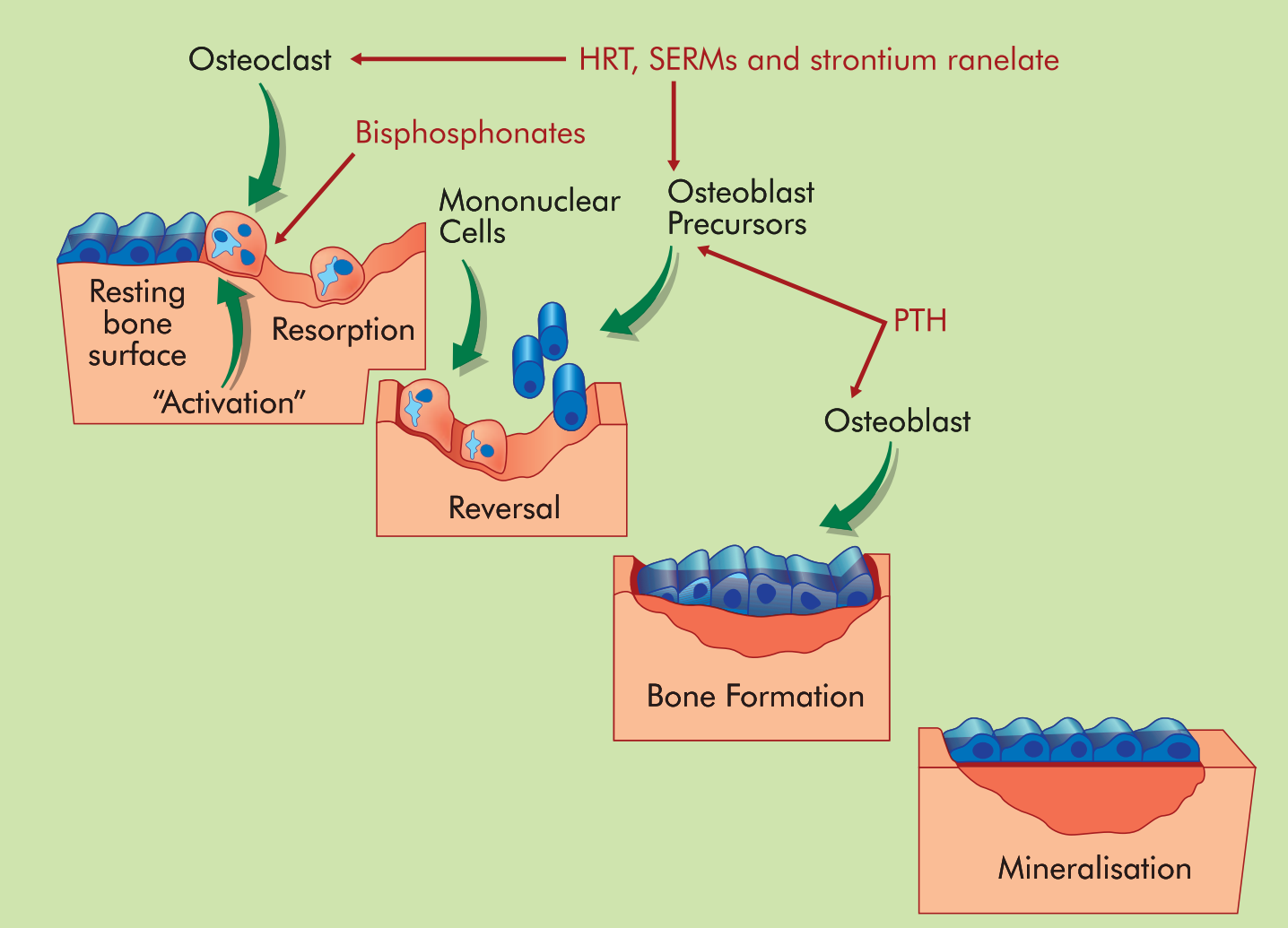


Figure 4 **Some sites of action of major treatments for osteoporosis. Bone is remodelled through digestion by osteoclasts, followed by the laying down of new bone matrix by osteoblasts and remineralisation.**

Amgen's compound AMG-162 (denosumab) represents a new approach to the problem of bone destruction in osteoporosis. It is a **monoclonal antibody** that is directed against a naturally occurring regulator of bone resorption. It is in Phase 3 trials in osteoporosis and is also being studied in other disorders, such as rheumatoid arthritis, in which it may prevent bone destruction.

Other new approaches are in earlier phase trials. Novartis has an inhibitor of bone resorption (AAE 581) in Phase 2 trial, as does Merck Sharp & Dohme (MK-0822). GSK has another such inhibitor 462795 (relacatib) at Phase 1. Also at Phase 1 are other compounds from GSK (751689) and Ligand and TAP Pharmaceuticals (LGD2941).

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PAIN

What is pain?

Acute pain is a defence mechanism - a warning from the body that something is wrong, or that there is a risk of injury. Rare individuals born without a sense of pain usually have short lives and many injuries, because they have no warning mechanism. Chronic pain, however, serves no such purpose. Chronic pain may result from direct tissue injury and inflammation (e.g. arthritic pain), from traumatic or disease-related damage, or from the nervous system itself (*neuropathic pain*), for example, in diseases such as diabetes or following shingles (*post-herpetic neuralgia*).

Who does pain affect and what does it cost?:

Pain is a very common experience. Despite this, there are few reliable statistics about its impact and economic costs. A survey in 2003 of over 46,000 people in 16 European countries found that about one in five adults had experienced moderate to severe pain several times a week for at least six months (chronic pain). About one-third of those reporting chronic pain said that they were constantly in pain.

A UK survey found that the most common cause of pain was back pain (27 per cent), followed by arthritis (24 per cent), headache (16 per cent) and injuries (8 per cent). A separate survey conducted in three UK cities found that overall about 8 per cent of respondents had chronic neuropathic pain.

The British Pain Society has reported that back pain alone is estimated to cost the exchequer about £5 billion per year in direct and indirect costs, but the total cost of treating all forms of chronic pain is not known.

Present treatments and shortcomings

Management of chronic pain seeks to eliminate pain completely, while using the minimum amount of medication that prevents it recurring. Therapy often needs to be individualised, but generally follows the three-step 'pain ladder' established by the World Health Organisation in 1990.

1. **Non-opioid analgesics** (painkillers) such as paracetamol, or aspirin, or non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac, naproxen or selective cyclooxygenase-2 (COX-2) inhibitors are used first for treating musculoskeletal pain. (See *Osteoarthritis* and *Rheumatoid Arthritis*)
2. If this proves inadequate, a **weak opioid** such as codeine, dihydrocodeine or tramadol is added or substituted. In addition, steroids, local anaesthetics, anti-emetics or tranquillisers may be given to increase the effectiveness of these analgesics.
3. In severe, intractable pain, **strong opioids** such as morphine, oxycodone, hydromorphone, fentanyl and methadone are used. These include skin patches of

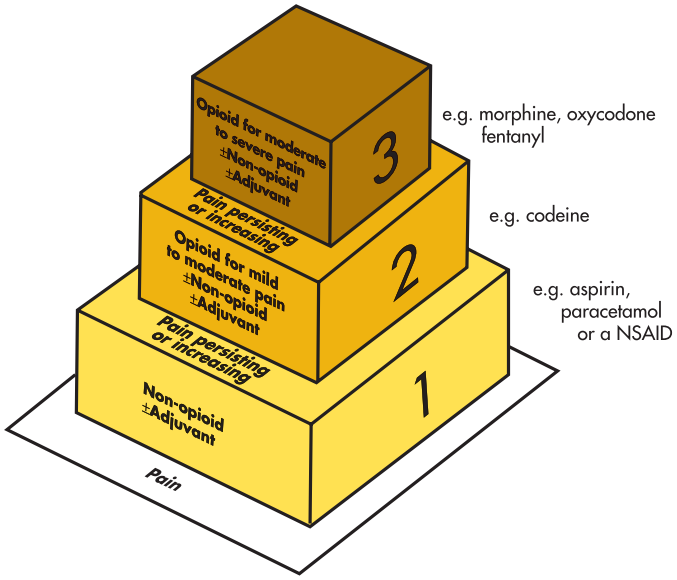

Figure 1 **The World Health Organisation's three-step pain ladder recommends a sequence of medicines of increasing strength to control pain**

fentanyl (Durogesic, Janssen-Cilag) and slow-release morphine, which give a more even and prolonged effect than injected or oral treatments. Opioids are often required for treating cancer-related pain.

Other medicines are available for treating types of neuropathic pain, such as trigeminal neuralgia and diabetic neuropathy. These include carbamazepine (Tegretol, Novartis), gabapentin (Neurontin, Pfizer), duloxetine (Cymbalta, Lilly) and pregabalin (Lyrica, Pfizer).

None of the existing analgesics (painkillers) is ideal. Strong opioids are addictive and can cause constipation. In severe pain, the doses required have a marked sedating action and affect respiration. Weak opioids such as codeine are only able to control mild to moderate pain. Non-opioid medicines such as aspirin and NSAIDs are only suitable for mild pain and may cause gastroduodenal ulcers. Many people have chronic pain that is difficult to control, or experience pain as the effect of their medicine wears off, and the need for better alternatives is clear.

What's in the development pipeline?

The sensation of pain is complex (Figure 2) and this gives considerable scope for developing medicines that act in new ways, or on different parts of the nervous system.

For example, GW Pharmaceuticals has several projects in progress to develop pain-relieving medicines based on **cannabinoids** that act on receptors in the nervous system. Delivered as a spray, one (Sativex) is being tested in cancer pain and in pain due to spinal cord injury (both in phase 3 trials), while another is in Phase 2 trial in post-operative pain. A fourth is in Phase 2 trial for pain

NEW SINCE 2000

2000 - Gabapentin (Neurontin, Pfizer) neuropathic pain

2001 - Buprenorphine TDS (Transtec transdermal, Napp)

2004 - Pregabalin (Lyrica, Pfizer) peripheral neuropathic pain

2005 - Duloxetine (Cymbalta, Lilly) diabetic neuropathic pain

2005 - Lumiracoxib (Prexige, Novartis) acute pain post-surgery

2006 - Ziconotide (Prialt, Eisai) severe chronic pain

originating in the nervous system. Others have also targeted cannabinoid receptors, with compounds from Novartis (SAD 448) and GlaxoSmithKline's GSK 842166 in Phase 1 and PRS-211,375 (Cannabinor, Pharmos) in Phase 2 trial.

Other compounds in Phase 2 trials that act in new ways include the calcium-channel blocker MK-6721 and the vanillin receptor-1 antagonist MK-2295, both being developed by Merck Sharp & Dohme, F-13640 from Pierre Fabre, Pfizer's monoclonal antibody PF-4383119 and the bradykinin antagonists Icatibant and SSR

Figure 3 **The peptide toxin from the marine cone shell is a compound in development for neuropathic pain that acts by a new mechanism**
Reproduced with the permission of David Paul and Prof Bruce Livett, University of Melbourne, Australia.

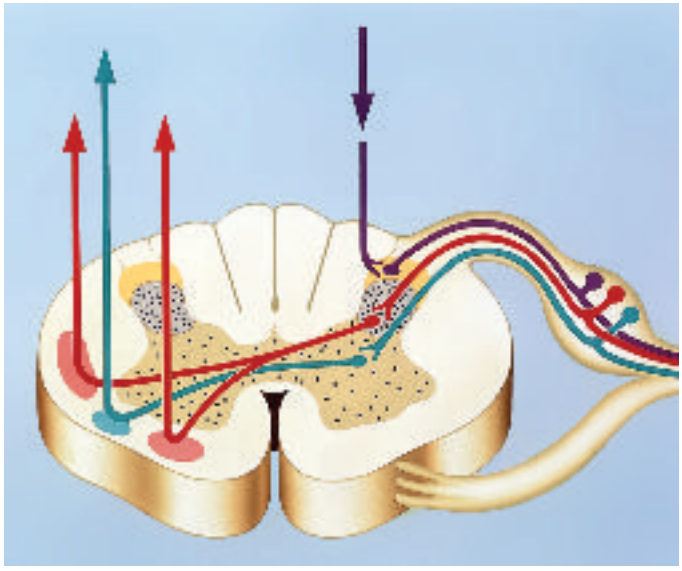

Figure 2 **Sensing pain involves both fast (red, acute pain) and slow (green, chronic pain) nerve fibres in the spinal cord, and is regulated by controlling neurons (purple) from the brain. This provides numerous targets for the development of new medicines.**

240612 from sanofi-aventis. Several companies also have compounds at this stage that act on opioid receptors, including Penwest (PW 4142), Vernalis (buprenorphine nasal spray, for post-operative pain) and Wyeth (methylnaltrexone - an opioid receptor antagonist that may reverse the action of opioids that cause constipation).

Neuropathic pain remains particularly difficult to treat, and there are a large number of new compounds undergoing clinical trials. Wyeth's desvenlafaxine is in Phase 3 study, as are Schwarz Pharma's lacosamide and Avanir's AVP 923, a combination of dextromethorphan and quinidine under study in diabetic neuropathy. Also at Phase 3 is NGX-4010, from Neurogesx, that is being developed for use in post-herpetic neuralgia.

Of the Phase 2 compounds for neuropathic pain, several act on nerve pathways involving the neurotransmitter glutamate. These include CNS-5161 from CeNeS Pharmaceuticals, and memantine and neramexane from Forest Labs, as well as Vernalis's V3381, in trial for diabetic neuropathic pain. Other compounds at this stage that act in new ways are Newron's ralfinamide, Takeda's TAK-583, and GSK's p38 kinase inhibitor GSK 681323.

One new compound which works in a different way comes from an unexpected source: the marine cone shell. One cone-shell toxin, ziconotide (Prialt, Eisai) is already available, and this works as a calcium-channel blocker. The new compound (ACV1, Metabolic Pharmaceuticals) has been shown instead to act by blocking a subclass of receptors in the nervous system.

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PARKINSON'S DISEASE

What is Parkinson's disease?

Parkinson's disease is a progressive, degenerative brain disorder, characterised by a loss of specialised nerve cells in parts of the brain called the *substantia nigra* and *locus coeruleus* and their connections. These cells contain the chemical messenger **dopamine** and become greatly depleted in advanced Parkinson's disease (Figure 1). Dopamine is involved in many functions, including the control of movement and co-ordination - in other words, Parkinson's is a dopamine deficiency disease.

The onset of Parkinson's disease is gradual. Common symptoms are slowness in initiating movement, muscular rigidity - which may lead to a loss of facial expression - and shaking (in about 70 per cent). More debilitating symptoms such as speech and swallowing difficulties, depression and constipation may emerge later. The rate of progression varies from 3-30 years and not all people develop the more severe symptoms.

Who does Parkinson's disease affect and what does it cost?

About 120,000 people in Britain are estimated to have Parkinson's disease and about 10,000 new cases are diagnosed annually. It most commonly affects those aged 50 or over and becomes more common with age, but younger people can also develop the disease. A study in 1998 found that the average cost of care for somebody with Parkinson's disease was nearly £6,000 per year. NHS costs accounted for 38 per cent of this cost, social care costs for 34 per cent and medication costs 24 per cent in those aged under 65. Costs increased dramatically with increasing disease severity, from an average of £2,971 a year in early disease to £18,358 a year at the most advanced stage.

NEW SINCE 2000

2000 - Rasagiline (Azilect, TEVA)

2005 - Rivastigmine (Exelon, Novartis) dementia in Parkinson's

2006 - Rotigotine TDS (Neupro, Schwarz)

2006 - Co-careldopa (Duodopa, Solvay)

Present treatments and shortcomings

Dopamine does not pass from blood into the brain and so cannot be given directly. Instead, a chemical called L-dopa is used, which does enter the brain and is converted there into dopamine (Figure 2). This transformation is brought about by the enzyme dopa decarboxylase (DDC), which is also present in tissues outside

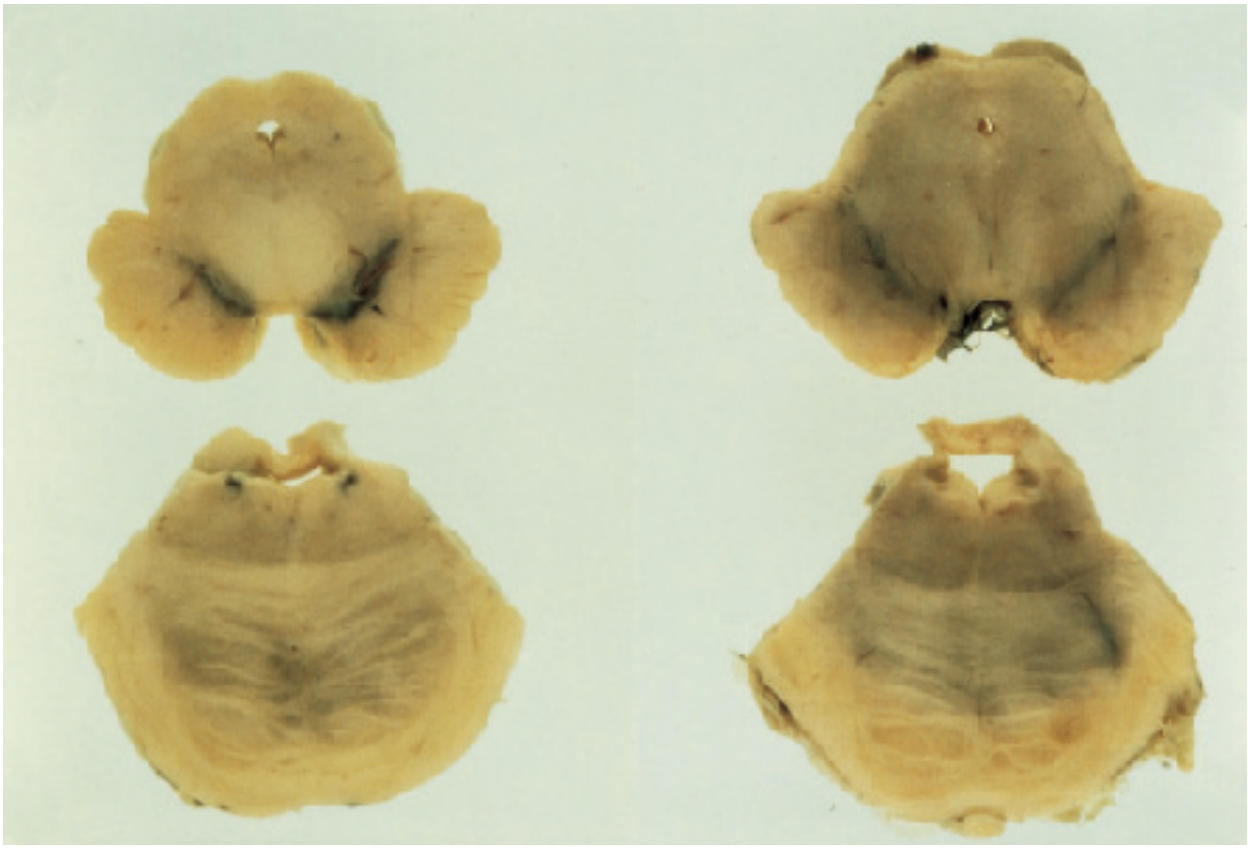

Figure 1: **Brain section showing loss of pigment in the substantia nigra**
(Courtesy of the Institute of Neurology)

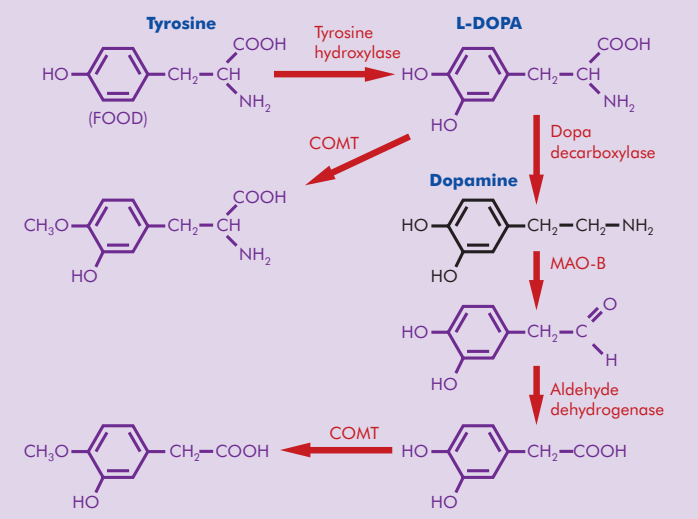

***Figure* 2: The formation and breakdown of L-DOPA and dopamine. The enzymes catalysing each step are shown in red**

the brain. Formation of dopamine in the general circulation leads to troublesome side-effects such as involuntary jerky movements (dyskinesia), and L-dopa is therefore given in combination with a DDC inhibitor (benserazide or carbidopa) that does not cross the blood/brain barrier. Such combinations form the mainstay of initial treatment and are available from Roche (Madopar) and Bristol-Myers Squibb (Sinemet) and as an intestinally administered gel formulation (Duodopa, Solvay).

Dopamine is broken down by the enzymes *monoamine oxidase-B* (MAO-B), and *catechol-O-methyl transferase* (COMT). Blocking these enzymes therefore provides a way of enhancing the action of dopamine in the brain. The MAO-B inhibitors selegiline (Eldepryl, Orion) and rasagiline (Azilect, Teva) and the COMT inhibitors entacapone (Comtess, Orion) and tolcapone (Tasmar, Valeant) are used for this purpose, often in combination with L-dopa. A triple combination of L-dopa, carbidopa (a DDC inhibitor) and entacapone is also available (Stalevo, Novartis).

Unfortunately, in most people, L-dopa loses its effect within 5-10 years, as well as causing fluctuations in motor ability and jerky movements (dyskinesias), and alternative strategies are then needed. One is to use compounds that mimic dopamine and stimulate its receptor (dopamine agonists). Bromocriptine (Parlodel, Novartis) and pergolide (Celance, Lilly) act in this way. Other more specific dopamine agonists are also available; these are ropinirole (Requip) from GlaxoSmithKline, cabergoline (Cabaser, Pfizer), pramipexole (Mirapexin, Boehringer Ingelheim) and rotigotine (Neupro, Schwarz), the latter being applied as a skin patch.

What's in the development pipeline?

While L-dopa is not likely to be displaced soon from its central role, research continues into ways of improving current medical treatment. Novartis has the acetylcholinesterase inhibitor rivastigmine (Exelon), the first medicine to treat dementia in Parkinson's disease, and Eisai has donepezil (Aricept) in Phase 3 trial for this purpose. GlaxoSmithKline is developing an extended release formulation of its dopamine agonist ropinirole. In a recent trial, adding this medicine to standard therapy delayed the return of symptoms as medication wears off (so-called 'off time') by an average of more than two hours a day.

At Phase 3, Merck Serono has a new MAO-B inhibitor (safinamide) which is also an inhibitor of dopamine reuptake. Preliminary results indicate that it improves motor symptoms, but it has also shown an effect in improving cognition. Eisai is studying an agent (E-2007) that is directed to a type of glutamate receptor. Kyowa Hakko also has a new agent in Phase 3 trial (KW-6002, istradefylline) to reduce motor symptoms and this represents a completely different approach from current medicines. Other companies trying this approach are Vernalis (V2006) and Schering-Plough (SCH-63390), but these compounds are still in Phase 2.

Solvay also has a new oral agent (SLV308) in Phase 3 trial. This combines dopamine activity with effects on the neurotransmitters noradrenaline and serotonin that may help with common symptoms such as depression and anxiety. A survey has shown that 80 per cent of people with Parkinson's disease also experience depression, although nearly half did not discuss such symptoms with their doctor.

A number of other new approaches are being explored in Phase 2 trials. Acadia Pharmaceuticals has ACP-103, which is being investigated for treating the L-dopa-induced tremors and hallucinations that may develop with prolonged use. Faust Pharmaceuticals has a compound (FP0011) that acts on glutamate receptors and protects nerves. Juvantia Pharma has JP-1730 (fipamezole) for treating dyskinesias, and sanofi-aventis has SR 57667.

Parkinson's disease has been seen as one of the key areas in which gene therapy might be of benefit. Progress has, however, been slow and such projects are still at a relatively early stage. Oxford Biomedica is working on a lentivirus vector system (ProSavin) to introduce the genes necessary for dopamine production into brain cells. Ceregene has started phase 1 trials with an adeno-associated virus vector (AAV) delivery system containing the neurturin gene, which makes a protein that aids survival of dopamine-producing cells. Avigen is also using an AAV vector system in its AV201 project to deliver the gene for the enzyme dopa decarboxylase into the brain. Lastly, Neurologix has announced positive interim results in a Phase 1 trial of its agent NLX-P101 that uses the AAV vector to introduce a gene for the enzyme glutamate decarboxylase. This enzyme produces the major inhibitory neurotransmitter in the brain, gamma-amino-butyric acid (GABA). Patients treated in this way showed an improvement in motor function one year after treatment, indicating that this approach may be of value in those with advanced Parkinson's disease.

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PERIPHERAL VASCULAR DISEASE

What is peripheral vascular disease?

Peripheral vascular disease (PVD) is also known as peripheral arterial disease (PAD) and peripheral arterial occlusive disease (PAOD). It is atherosclerosis of the extremities sufficient to affect blood flow (see *Atherosclerosis*). At first, atherosclerosis may just reduce blood flow in the affected artery by narrowing the internal space, but in more advanced disease, flow may actually be halted by formation of a clot through the clumping of tiny blood cells called platelets and their entrapment in fibres of the insoluble blood protein fibrin (see *Thrombosis*). In this case, there may be growth of smaller blood vessels around the site of blockage that partially compensates for the blocked blood flow.

Peripheral vascular disease affects the legs eight times more often than the arms. Its most common symptom, *intermittent claudication*, shows as a pain in the leg (usually in the calf muscles) that develops on walking and subsides on resting. In another form of peripheral vascular disease, *critical limb ischaemia,* a severe pain develops in the lower leg/foot after going to bed that is relieved, at least initially, by hanging the leg out of bed. Poor circulation in critical limb ischaemia may lead to wounds and ulcers that do not heal, leading to gangrene and the need for amputation.

Pain in peripheral vascular disease has the same cause (inadequate blood-borne oxygen and nutrient supply to muscle because of atherosclerosis) as the pain of angina (see *Ischaemic Heart Disease*) and patients with peripheral vascular disease typically have a 2-3 times higher death rate from a heart attack or stroke than healthy people of the same age, especially if they also have diabetes. This increased risk of death is not unexpected since, if atherosclerosis is detectable in the arteries of the legs, it is also likely to be present in other parts of the body, such as the coronary artery and in the carotid artery leading to the brain.

Intermittent claudication may be progressive, limiting independent living. Eventually it may require angioplasty to open or widen the blocked artery, or vascular surgery to replace a section of blocked artery, or even amputation. Amputation will be necessary in the lifetime of only 2-4 per cent of those with intermittent claudication and in most patients, the disease can be treated medically. Raised blood triglyceride levels, smoking and diabetes are all important risk factors for disease progression, stroke and heart attack (See *Ischaemic Heart Disease*).

Who does peripheral vascular disease affect?

Peripheral vascular disease is unusual before the age of 50, but its prevalence rises with increasing age. In a survey of over 1,500 men and women aged 55-74, the overall prevalence of intermittent claudication was 4.5 per cent. However, the number of people with symptomless peripheral vascular disease is much greater - almost two-thirds of people in this age range. It has been estimated

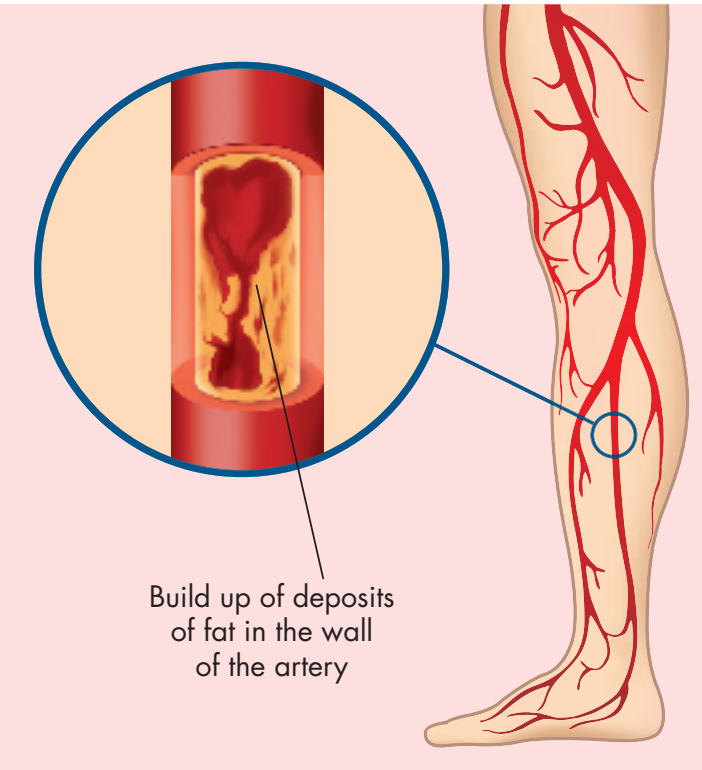

***Figure* 1: Narrowing or blockage of a major artery in the leg is the cause of intermittent claudication**

that over 100,000 people are diagnosed with peripheral vascular disease each year in the United Kingdom. PVD was recorded as the underlying main cause of 2,384 deaths in England and Wales in 2004, almost 85 per cent of them in people aged 75 and over, but many PVD-related deaths are likely to have been recorded under figures for stroke or heart attack.

Present treatments and shortcomings

Non-emergency treatment of peripheral vascular disease has three aspects: managing the symptoms that degrade quality of life, addressing risk factors of the underlying atherosclerotic process and preventing cardiovascular complications. Aggressive treatment of lifestyle factors (e.g. smoking cessation, weight loss) and intervention to manage diabetes and reduce blood pressure and high lipid levels is essential to prevent disease progression (see *Atherosclerosis, Diabetes* and *Hypertension*) but there is evidence that not all PVD patients currently receive adequate treatment.

Relatively few medicines have been authorised specifically for the treatment of intermittent claudication. Inositol nicotinate (Hexopal, Genua) is a medicine that causes blood vessels to dilate or expand (a vasodilator) that may reduce vascular resistance to blood flow and cilostazol (Pletal, Otsuka) is both a vasodilator and an agent that stops platelets sticking together. Pentoxifylline (Trental, Sanofi-aventis) improves the flow properties of blood, thinning the blood and increasing red blood cell flexibility. Naftidofuryl oxalate (Praxilene, Merck Sharp & Dohme) enhances the way muscle uses glucose and oxygen, making better use of the available blood supply. The improvements in pain-free walking distance achieved with these medications is usually modest (40-50 per cent) and side-effects such as nausea, rashes and drowsiness may be

observed. A regime of exercise training should accompany medical therapy and may sometimes be more effective.

What's in the development pipeline?

Several new **anti-platelet agents** are in development for peripheral vascular disease. Nissan Chemical has reported positive results (increase in walking time) in a Phase 2 study of its NM-702 in the treatment of intermittent claudication. Another similar compound is Endovasc's Liprostin. This showed a significant increase in walking distance in a Phase 2 trial in patients with intermittent claudication and is now in preparation for Phase 3 studies. Two other anti-platelet agents under study are DG041 (DeCode Genetics, Phase 2) and Kowa's K-134 (Phase 1), which has an inhibitory effect on blood vessel wall thickening.

New **thrombolytic agents** are also being tried in peripheral vascular disease. Menarini has amediplase in Phase 3 trial. In addition, ThromboGenics has microplasmin in Phase 2 study, and Wyeth has PAI-749 (diaplasinin) in Phase 1 trial.

Among other approaches, sanofi-aventis has a compound (SL 65.0472) that interacts with serotonin receptors and a guanylate cyclase activator (HMR 1766, ataciguat), both at Phase 2.

The longer-term future

There have been a number of attempts to use **gene therapy** in peripheral vascular disease. These projects typically aim to promote the growth of new blood vessels to bypass an obstructed artery. Several companies (sanofi-aventis, Daiichi-Sankyo, Genzyme) have projects of this type in Phase 2 trials. Lastly, Cardium Therapeutics has an agent (Genvascor) based on the enzyme endothelial nitric oxide synthase (eNOS) that, by increasing local production of artery-relaxing nitric oxide, may alleviate ischaemic pain in critical limb ischaemia. This project is still at the pre-clinical stage.

While these gene therapy approaches do not cure the blockage that causes symptoms, they may provide a relatively simple way of improving functional status that would bring welcome relief in patients whose lives are limited by peripheral vascular disease.

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PSORIASIS

What is psoriasis?

Psoriasis is a chronic inflammatory skin disorder characterised by red disc-like raised lesions with dry, silvery scaling, most frequently on the elbows, knees or scalp. There are periods when psoriasis flares up (a *relapse*) and quieter periods (*remissions*) The lesions build up because the rate of cell division of psoriasis skin is much higher than normal. Most cases are mild, but a few can be widespread and disfiguring. The cause of psoriasis is not known, but a genetic component and involvement of the immune system have been implicated. While not curable, treatment can bring periods of remission and improve both appearance and mood.

Who does psoriasis affect?

Psoriasis is thought to affect approximately two per cent of the population of the UK, but some people with mild psoriasis of limited extent may not seek medical help and hence go undetected. The disease usually occurs in young adults (15-40 years, with an average age of onset of 33), with men and women equally likely to be affected. About 5-10 per cent of people with psoriasis develop a form of arthritis. Psoriatic arthritis most often affects the joints of the fingers and toes and is somewhat more common in women than men.

Present treatments and shortcomings

Mild to moderate skin plaques are traditionally treated with formulations applied to the skin (known as *topical* preparations) containing either dithranol or coal tar and colloidal sulphur. Ointments containing the vitamin D derivatives calcipotriol (Dovonex, Leo), calcitriol (Silkis, Galderma), tacalcitol (Curatoderm, Crookes) or the vitamin A derivative tazarotene (Zorac, Allergan) are used to treat chronic plaques. Steroids applied to the skin are also frequent first-line treatments, but inflammation may recur when they are stopped. A combination of calcipotriol and the steroid betamethasone (Dovobet, Leo) is available for early use. Antibacterial and antifungal solutions may be useful in preventing infection of the inflamed skin.

NEW SINCE 2000

2001 - Calcipotriol + betamethasone ointment (Dovobet, Leo)

2004 - Efalizumab (Raptiva, Serono)

2004 - Etanercept (Enbrel, Wyeth)

2005 - Infliximab (Remicade, Schering-Plough)

Exposure to certain wavelengths of ultraviolet light while simultaneously taking psoralen, and the vitamin A derivative acetretin (Neotigason, Roche) can be beneficial in some cases. In severe psoriasis, the immunosuppressive medicines methotrexate and cyclosporin are effective, but cause general immunosuppression. Three biological treatments (medicines based on proteins) have also been authorised for use where other therapies have been ineffective - etanercept (Enbrel, Wyeth) and infliximab (Remicade, Schering-Plough), both of which are directed against Tumour Necrosis Factor alpha (TNF-α) which causes inflammation, and efalizumab (Raptiva, Serono).

None of the many treatments for psoriasis is entirely satisfactory. Many topical preparations are messy and slow-acting (4-6 weeks) and none eradicate the condition: relapse is inevitable. Acetretin persists in the body for a long time and can cause birth defects, so women of child-bearing age are warned not to become pregnant for two years after a course of treatment. Those using anti-TNF-α preparations must also be monitored carefully for serious infections, especially tuberculosis.

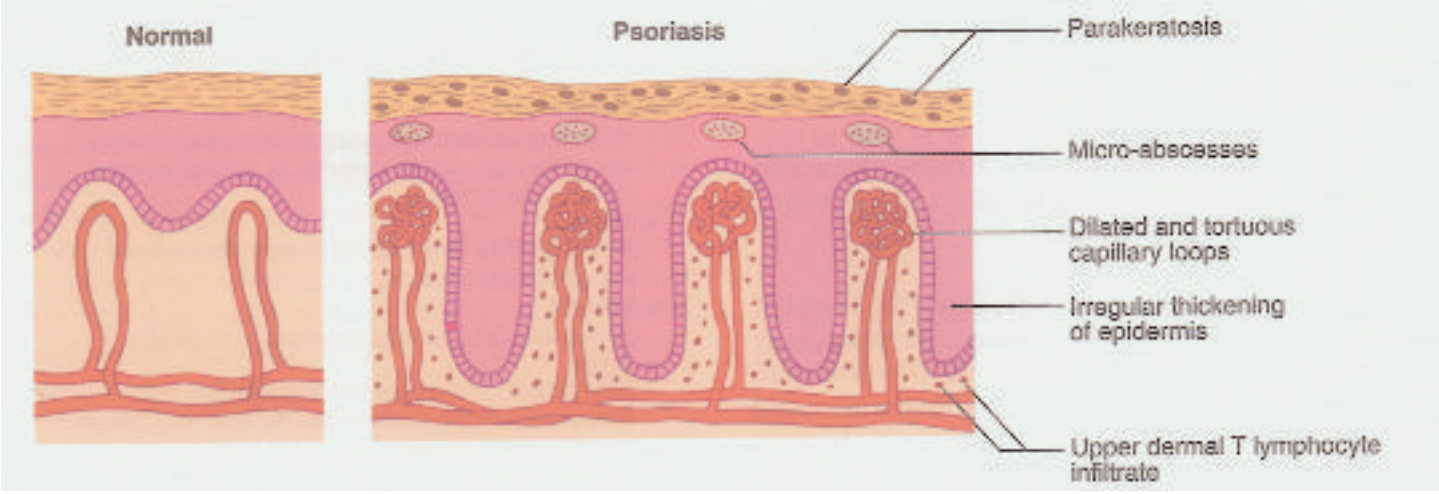

***Figure* 1: Characteristic changes to skin structure can be seen by microscopy in psoriasis**
Reprinted from Davidson's Principles and Practice of Medicine

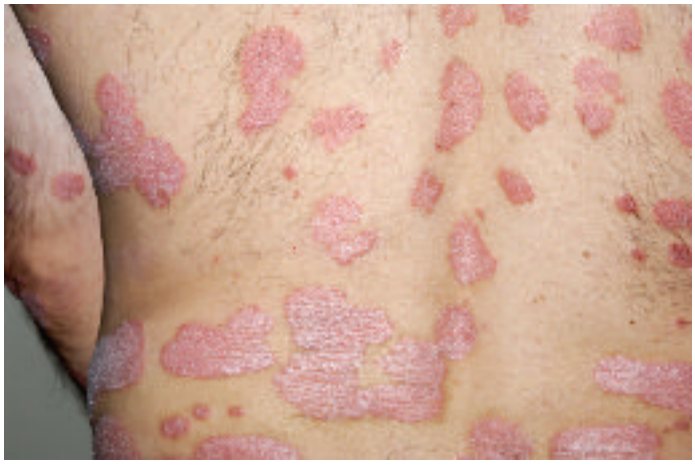

Figure 2: **Plaque psoriasis on a man's back**

What's in the development pipeline?

Several more biological agents are in development. Nearest to becoming available is alefacept (Amevive, Astellas), a human fusion protein. Adalimumab (Humira, Abbott), a human anti-TNF-α monoclonal antibody that is already indicated for use in psoriatic arthritis, is also in late Phase 3 trial. In a study, nearly 80 per cent of patients treated with adalimumab achieved a reduction of 75 per cent or better in their psoriasis area and severity index (PASI) rating, compared with 35.5 per cent of those treated with methotrexate and 18.9 per cent of those given placebo. Other monoclonal antibodies in development include certolizumab pegol (UCB), an anti-TNF-α preparation, Centocor's CNTO-1275 (both at Phase 3) and ABT-874 (Abbott), which is at Phase 2.

Several new oral agents are in development:

- Isotechnika has ISA247 in Phase 3 trial. It appears to be better tolerated than other immunosuppressants, with little effect on kidney function or blood lipids. Patients with moderate to severe psoriasis experienced an average reduction in PASI score of 60 per cent over 24 weeks of treatment with this compound, and scores continued to improve over an additional 36 weeks.
- Biogen Idec's BG-12 is also in Phase 3 development. Patients taking this compound experienced a 68 per cent reduction in PASI after 16 weeks, as compared with a 10 per cent fall in those given placebo.
- Celgene has an anti-inflammatory compound (CC-10004) in Phase 2 trial in severe psoriasis
- Advitech has a growth factor-containing preparation (XP-828L) that has shown efficacy in mild-to-moderate psoriasis. It is derived from milk protein.

Other new Phase 2 compounds are being developed for topical administration:

- Cytochroma Inc has a new vitamin D analogue (CTA018)
- Leo has two compounds, 80185 (Phase 2 for body psoriasis and Phase 3 for scalp psoriasis) and 80190 (Phase 2 for facial psoriasis) that are also based on vitamin D
- Revotar Biopharma is investigating bimosiamose
- Vitae Pharmaceuticals has VTP-201227, which acts on two enzymes present in the skin that may be involved in healing of psoriatic lesions
- York Pharma is testing carbenoxolone
- Zelos Therapeutics is investigating topical use of Ostabolin-C.

The introduction of biological treatments has given a welcome stimulus to the development of new compounds for psoriasis. Although the causes and processes of the disease are still not well understood, these newer compounds focus on molecules that are known to be involved in its progress, and are more specific in their actions than older medicines such as steroids, vitamins and coal tar. There is, therefore, good hope of future treatments giving better control of symptoms with fewer troublesome side-effects and greater convenience in use.

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Website: www.thepaa.org

RESPIRATORY INFECTIONS

What are respiratory infections?

Respiratory infections affect the nasal passages, throat, larynx and lungs. They can be caused by bacteria, viruses or, less commonly, by fungi or rickettsia. Laryngitis, tonsillitis, bronchitis, influenza, the common cold, and pneumonia are well-known examples of respiratory infections. Bacterial infections in the lungs may be chronic, as in people with cystic fibrosis or bronchitis, and are often very resistant to antibiotics. Common bacteria causing lung infections are various streptococci and *Haemophilus influenzae*. Pseudomonas is especially problematical in cystic fibrosis (see *Bacterial Infections* and *Cystic Fibrosis*). This section, however, deals primarily with respiratory diseases caused by viruses.

Influenza (Figure 1) is a virus with three major subtypes (A, B and C) that causes potentially serious respiratory infections and periodically causes epidemics or even pandemics (world-wide epidemics). Type A influenza virus is the most common cause of influenza in humans and can also infect birds (avian flu). The pandemic influenza of 1918/19 has recently been shown to have originated in birds and it is feared that if current strains of avian flu in poultry and wild birds acquire the ability to spread from one human being to another, this could cause another pandemic of similar seriousness.

Another virus (a coronavirus) has been found to be responsible for the viral pneumonia known as severe acute respiratory syndrome (SARS), which also has a high death rate. Other important respiratory viruses are less well known. They include respiratory syncytial virus (RSV), which causes inflammation of the airways in about 20,000 infants each year and may lead to pneumonia, and cytomegalovirus (CMV), which can cause a type of pneumonia in those with a depressed immune system.

Who do respiratory infections affect?

It has been estimated that 120 million people get influenza every year in the US, Europe and Japan. During a pandemic, very many people may die, especially the very young, infirm and elderly. Over 20 million people are estimated to have died worldwide during the great influenza pandemic of 1918/19. Pneumonia is a leading cause of death, especially among the elderly - 30,649 deaths in England and Wales in 2004 were recorded as being primarily due to pneumonia, 87 per cent of these being in those aged 75 and over. Many cases of pneumonia are due to bacteria, but the specific infection is rarely recorded on death reports. The yearly number of influenza-related deaths is uncertain.

Present treatments and shortcomings:

Over-the-counter medicines such as aspirin and decongestants provide relief of symptoms and reduce fever, but there are no medicines that cure either the common cold or influenza. Amantadine (Lysovir, Alliance) is available for the prophylaxis and treatment of flu, but is mainly used in those at risk, such as

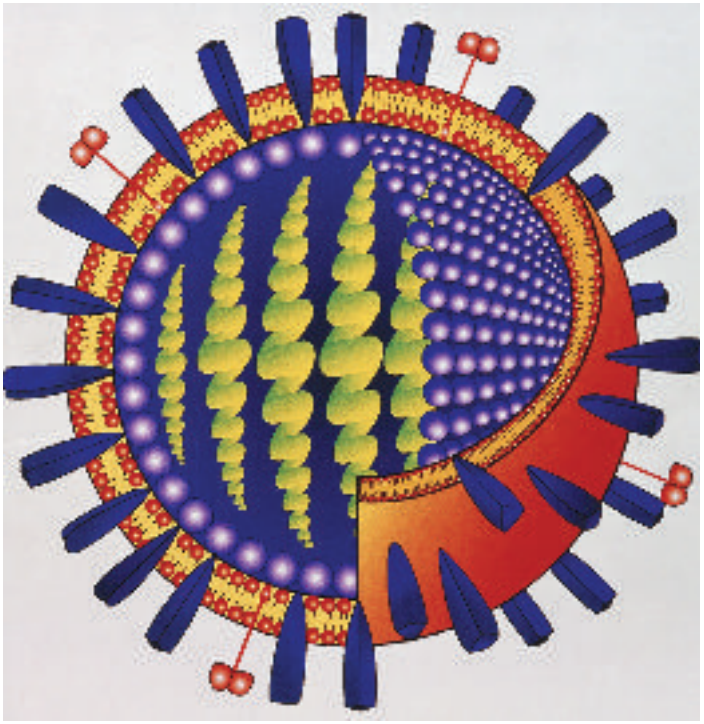

***Figure* 1: The influenza virus carries on its surface haemagglutinin molecules (blue), by which it adheres to cells in the respiratory tract, and neuraminidase (red), involved in the release of new virus particles. Both mutate rapidly, so that a new vaccine is needed each year.**

immunocompromised patients, as the benefits are too modest for general use. It is only active against Type A flu viruses, which account for 65 per cent of outbreaks. Two neuraminidase inhibitors are available for the treatment of the symptoms of influenza, which must be started within 48 hours of the first appearance of symptoms. One, zanamivir (Relenza, GlaxoSmithKline), is inhaled. It shortens the period of symptoms only modestly and can induce contraction of the airways and serious respiratory deterioration in patients with asthma or chronic obstructive pulmonary disease. The other, oseltamivir (Tamiflu, Roche), is taken by mouth. Both are indicated for the prevention as well as treatment of influenza. Nausea, vomiting and gastric pain, mainly on first starting treatment, were the most common adverse reactions to oseltamivir seen in clinical trials.

Prevention of influenza depends on the rapid production of vaccines tailored to the specific strain at the first signs of an epidemic. Each vaccine is, in effect, a new product each year. A variety of preparations are available for use in the UK, including vaccines from GlaxoSmithKline, Novartis, Wyeth, Solvay, and Sanofi Pasteur MSD.

The monoclonal antibody palivizumab (Synagis, Abbott) can be used to prevent RSV infections in children at high risk for RSV disease, but is considered too expensive for more general use. Ribavirin (Virazole, Valeant) is currently the only medicine for the treatment of RSV infections.

What's in the development pipeline?

Only a few compounds are in development for treating respiratory infections due to viruses. A nasal spray formulation of the antiviral pleconaril is in Phase 2 development by sanofi-aventis for treating the common cold. Daiichi-Sankyo has CS-8958 in Phase 1 trial for influenza infections. NexBio is preparing Phase 1 studies with NEX-DAS181 (Fludase), which is designed to prevent influenza virus entering and infecting airways cells. BioCryst's injected peramivir is also in Phase 1 study, as is Alnylam Pharma's ALN-RSV01, which is designed to treat RSV. Novartis also has an antiviral (RSV604) against RSV in development which has reached Phase 2.

Intensive research is, however, going into the development of new flu vaccines. The main aspects can be summarised as the development of:

- seasonal flu vaccines, some combined with other compounds to increase their effect
- vaccines against pandemic flu
- cell culture-based production methods.

Adjuvants have been used for many years in other vaccines. They are substances that stimulate a stronger antibody response and are used to increase the effectiveness of vaccines. GlaxoSmithKline and Novartis both have **seasonal influenza** vaccines in Phase 3 trial that contain new adjuvants.

The use of an adjuvant will be particularly important in vaccines against **pandemic flu**, as there will be a great need to vaccinate the largest possible number of people as rapidly as possible following the start of a pandemic, and this will mean using vaccines with the maximum effect. Both Novartis and GSK are therefore also incorporating adjuvants into their experimental vaccines directed against the H5N1 strains of pandemic flu. Both companies are working with the regulatory authorities in advance of the appearance of human pandemic strains, in order to reduce as far as possible the time needed for review once this emergency situation arises.

Cell culture-based production methods will also be of great importance in the response to a flu pandemic. Virus growth in chicken eggs, as at present, is difficult to scale up and takes several months to produce sufficient quantities for vaccine production. Cell culture methods are quicker, more flexible and more easily controlled. Novartis has a seasonal flu vaccine made by cell culture on a mammalian cell line (MDCK cells) and Solvay has built a new plant for producing its own seasonal flu vaccine on the same cells. Solvay is also developing a nasal spray form of its vaccine that has reached Phase 2 trial. Baxter has a cell production system that has already been used to make vaccine against smallpox, and this is now being used to produce a stockpile of whole-virus (H5N1) pandemic flu vaccine (Phase 2) under contract for the NHS.

Sanofi-Pasteur is now developing PER.C6 cell line technology to produce both seasonal flu vaccine and experimental (H7N1) pandemic flu vaccines (both at Phase 1). (The company also has an experimental H5N1 vaccine in Phase 2 trials that is made by the standard chicken-egg process). Crucell has three vaccines based on the H9N2 strain of avian flu grown by the cell culture method in Phase 1 trial.

Lastly, two interesting developments are still at the pre-clinical stage:

- Vical is developing an adjuvant-containing DNA vaccine, based on avian flu virus surface protein, which could be grown by fermentation methods
- Acambis has started development of a 'universal' flu vaccine, directed against the M2 surface protein of the influenza A virus and which shows little variation between strains. If this approach were successful, it would remove the need to create a new vaccine each year.

Such developments raise exciting prospects for the future of influenza vaccination. However, the threat of a pandemic is very real, and this could start at any time if an unlucky mutation in the avian flu virus should produce a strain that can easily be passed from one human being to another. It must therefore be hoped that some at least of the projects just discussed come to fruition very quickly.

RHEUMATOID ARTHRITIS

What is rheumatoid arthritis?

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints. Persistent inflammation initially affects the synovium of the movable joints of the skeleton (Figure 1). With the passage of time, the synovium thickens to form *pannus* tissue which invades cartilage and bone. Among the earliest joints affected in many people are those of the hand, where small cavities can be detected using microfocal X-ray methods (Figure 2). As well as affecting the joints, RA can damage connective tissue in many other body systems, such as the skin, lungs, nerves, blood vessels and heart. For that reason, it is often referred to as rheumatoid disease. A study of a group of people with RA who were monitored for 40 years showed that RA reduced average life expectancy by about 10 years as compared with people who did not have RA, with the leading cause of death being cardiovascular disease.

The rate of progression of RA is very variable: a few people have an aggressive form of the disease, leading to disability in months, while in most people it takes years. Ultimately, the cartilage is destroyed, causing pain, as bone grates against bone, and causing bleeding into the joint. There is loss of function as tendons become displaced from their normal position, shorten, and cause the characteristic joint deformities of the disease.

The cause of RA remains unclear, but it may be an autoimmune disease, in which damage is caused by the body's immune system mistakenly attacking its own tissue. Some kinds of infection seem to trigger this attack, especially in people who have a family history of RA, suggesting that they have predisposing genes.

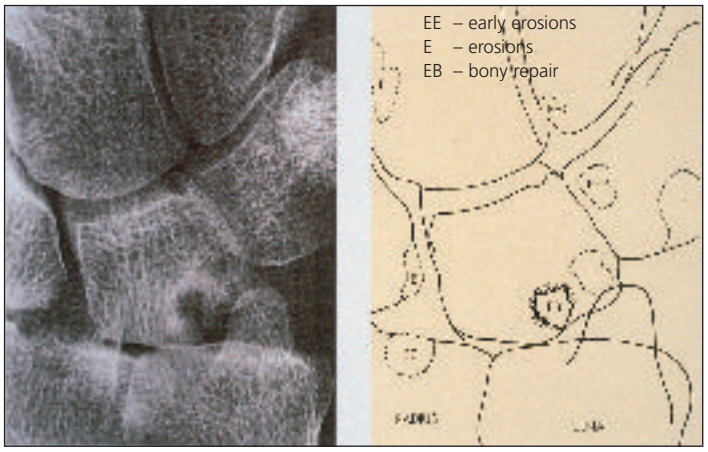

***Figure 2*: X-ray of the hand in early RA**
(Courtesy Prof. C Buckland-Wright)

Who does rheumatoid arthritis affect and what does it cost?

RA affects about 0.8 per cent of the adult population in the UK, or 387,000 people. It is over twice as frequent in women as in men, and starts most often in the child-bearing years. In addition, 12,000 children in the UK have the related inflammatory disease juvenile idiopathic arthritis. The Office of Health Economics estimates that treatment of rheumatoid arthritis and related conditions cost the NHS £792 million in 2002/03, but this figure does not include lost earnings, and costs of non-professional carers, social services etc, so that the total cost to society is likely to exceed £1 billion per year.

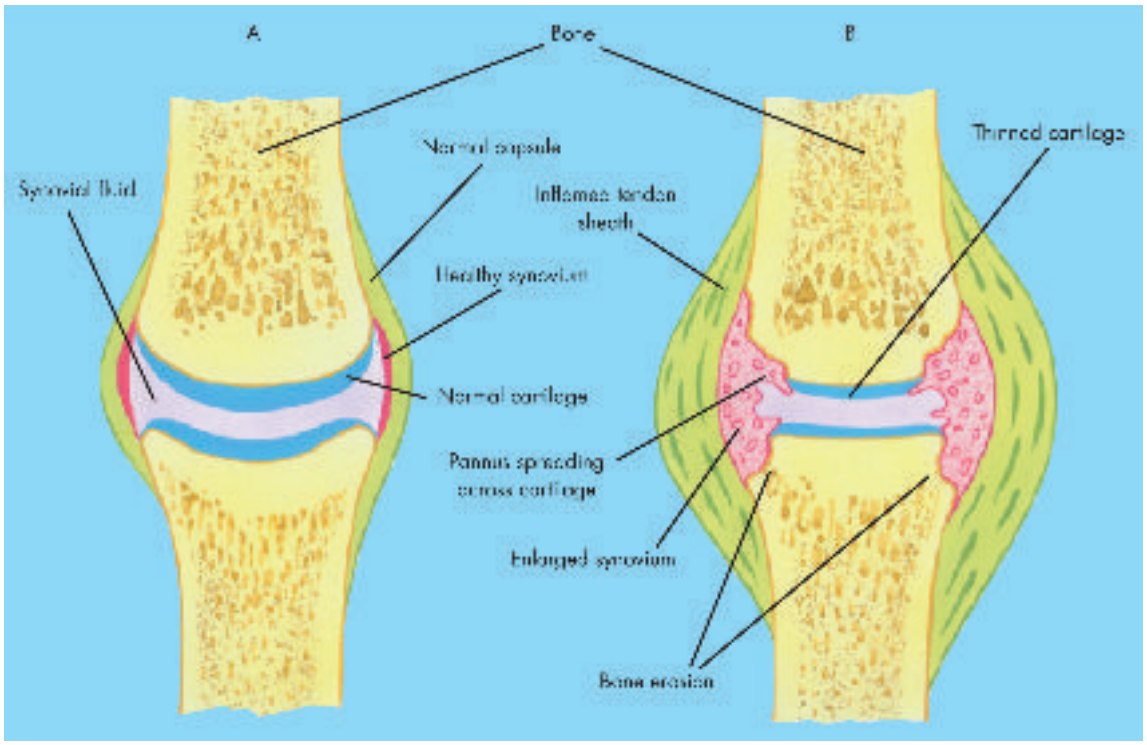

***Figure 1*: Diagram of a normal (A) and an RA joint (B).**

Present treatments and shortcomings

Rheumatoid arthritis involves three processes that are targets for treatment. For some reason, RA causes chronic activation of the immune system, resulting in production of an autoantibody called 'rheumatoid factor', which can be found in the circulation and in affected joints. White blood cells then enter the joint and release substances including interferon gamma (IFN-γ) and *cytokines*, especially IL-1, IL-6, and TNF-α (Figure 3), that cause **cell proliferation**, resulting in synovial thickening and pannus formation. Cytokines are a product of cells of the immune system that stimulate immunity. Cytokine-induced **inflammation** causes the release of further substances in the synovium that cause pain, tenderness and swelling around the joints. Finally, enzymes in the joint and at the pannus-cartilage interface cause **destruction** of the cartilage and underlying bone.

An area of early success for medicines research was the development of compounds to treat the **inflammation** in RA. Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors work by inhibiting the enzyme cyclo-oxygenase (COX), now known to exist in two forms: COX-1 and COX-2. This reduces the formation of inflammatory prostaglandins. Individuals differ in their response to NSAIDs and, as there are many different types, several can be tried until the best one is found. Some of the best known NSAIDs are diclofenac (Voltarol, Novartis), flurbiprofen (Froben, Abbott), ibuprofen (Brufen, Abbott), meloxicam (Mobic, Boehringer Ingelheim) and naproxen (Naprosyn, Roche). All are available for use in the more commonly occurring osteoarthritis as well as in RA.

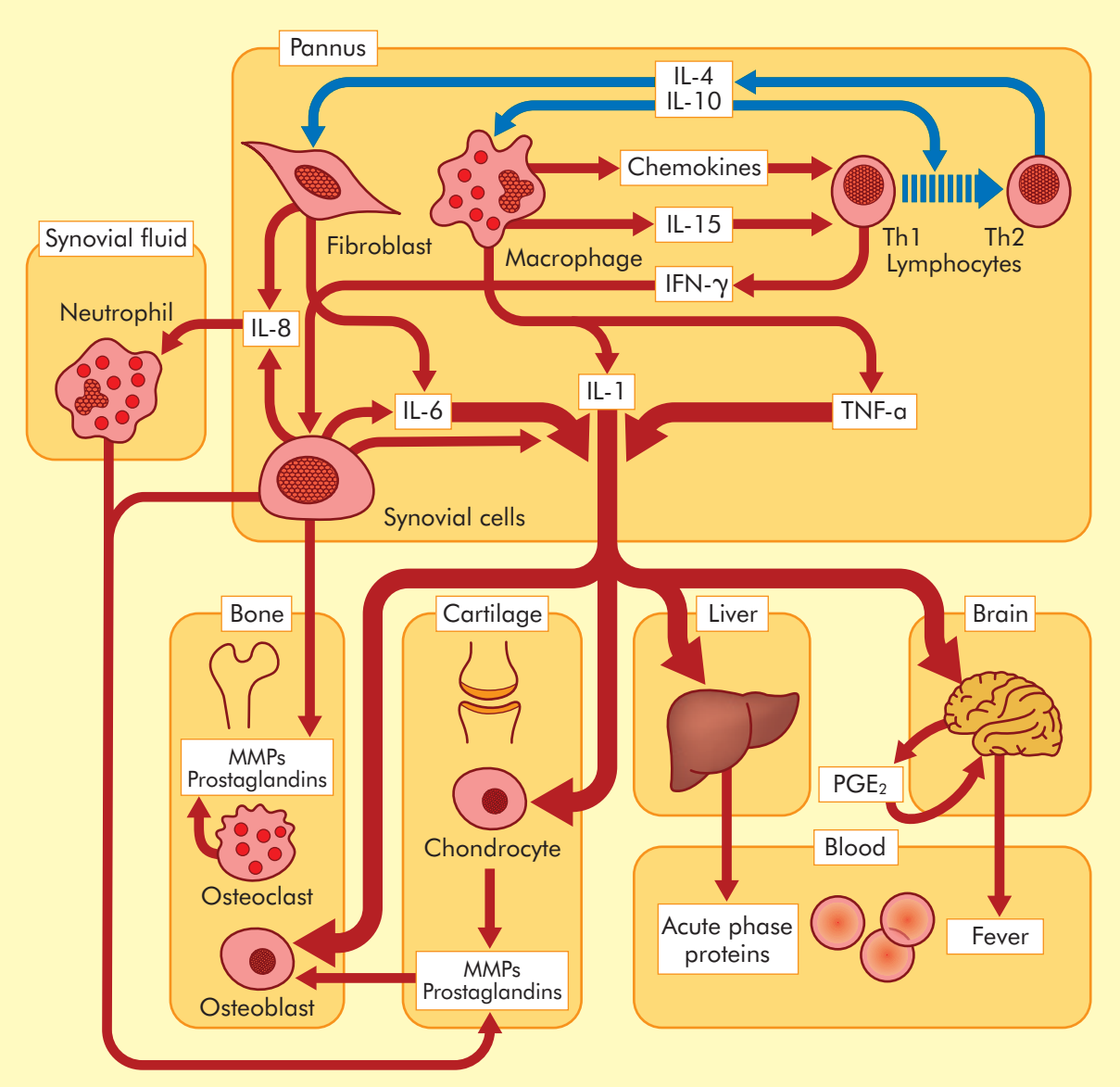

***Figure* 3: Some of the processes thought to contribute to the pathology of RA.**
Reprinted from Davidson's Principles and Practice of Medicine.

NEW SINCE 2000

2000 - Celecoxib (Celebrex, Pfizer)
2000 - Infliximab (Remicade, Schering-Plough)
2000 - Etanercept (Enbrel, Wyeth)
2002 - Etoricoxib (Arcoxia, Merck Sharp & Dohme)
2002 - Anakinra (Kineret, Amgen)
2003 - Adalimumab (Humira, Abbott)

Older, non-selective NSAIDS can cause serious stomach bleeding. About 20 per cent of gastroduodenal ulcers are caused by NSAIDs and the cost to the NHS of treating their side-effects has been estimated to be as much as £1 million per day. It is now known that prostaglandins produced by COX-1 protect the stomach, while those formed by COX-2 cause inflammation. Hence, compounds that specifically block the action of COX-2 but not COX-1 should control inflammation without harming the stomach. Two selective COX-2 inhibitors, celecoxib (Celebrex, Pfizer) and etoricoxib (Arcoxia, Merck Sharp & Dohme), are available for use in RA. However, caution is recommended in their use, as some earlier selective COX-2 inhibitors, now withdrawn, have been shown to be associated with an increased risk of complications such as heart attack and stroke.

Attempts to find medicines that slow or halt **proliferation** have, however, been less successful. *Disease Modifying Anti-Rheumatic Drugs* (DMARDs), of which the most often used are methotrexate (Maxtrex, Pfizer) and sulfasalazine (Salazopyrin, Pfizer), have been available for many years, but are not always effective. The newer leflunomide (Arava, sanofi-aventis) and cyclosporin (Neoral, Novartis) are of value in severe disease, but may cause serious side-effects. Recently, it has been recognised that DMARDs are most beneficial when given early in the disease process, together with an NSAID. Used in this way, the combination damps down inflammation and slows down the growth of pannus and thickening of tendons, but does not entirely prevent them.

The newest anti-proliferative medicines are three that inhibit tumour necrosis factor alpha (TNF-α), which has an important role in inflammation. Etanercept (Enbrel, Wyeth) is a soluble TNF-α receptor that binds to and inactivates TNF-α, and infliximab (Remicade, Schering-Plough) and adalimumab (Humira, Abbott) are anti-TNF-α monoclonal antibodies. They are available for use late in the disease, in patients who have failed to respond to other DMARDs, and are given by injection. However, blocking TNF-α also has an immunosuppressive effect and there have been reports of increased infection rates with their use. Patients will normally be screened for latent tuberculosis and treatment will also be withheld if there is evidence of other active infections. Infliximab has also been found to contribute to heart failure and is unsuitable for those at risk.

Those with severe active RA who have not responded to DMARDs and anti-TNF-α agents can be given rituximab (MabThera, Roche),

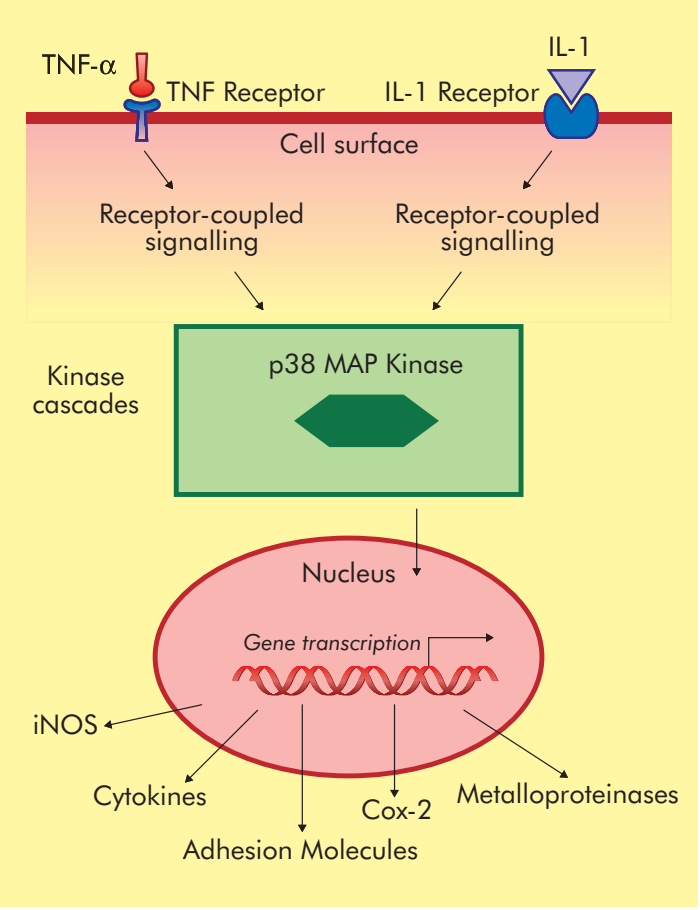

***Figure* 4: Kinase signalling controls the production of a wide range of inflammatory molecules produced in cells involved in joint inflammation.**

which is also used to treat non-Hodgkin's lymphoma. In a Phase 3 study, 51 per cent of those treated with rituximab experienced at least a 20 per cent improvement in clinical signs of disease activity, as compared with 18 per cent of those treated with placebo.

Finally, anakinra (Kineret, Amgen) an inhibitor of the pro-inflammatory cytokine interleukin-1, is available for treating RA that does not respond adequately to the DMARD methotrexate alone. However, NICE has recommended that it should only be used in the context of a clinical study.

There are no medicines currently on the market which control ***tissue destruction*** in late-stage RA.

What's in the development pipeline?

Efforts to develop alternative NSAIDs and selective COX-2 inhibitors have essentially ceased, but there are ongoing projects to develop other medicines that interact with TNF-α. Two are at the Phase 3 stage: certolizumab pegol (Cimzia, UCB), and golimumab (Centocor/Schering-Plough). Both are intended for use in moderate to severe RA. A so-called TACE inhibitor (BMS-561392) from Bristol-Myers Squibb is at Phase 2. At Phase 1, Targeted Genetics is exploring another approach with tgAAC94 - a gene therapy product that seeks to introduce the gene for soluble TNF-α receptor protein into affected joints.

A variety of other projects aim to block one or more of the other **cytokines** that fuel the inflammatory reaction in RA. Amgen's AMG-108 (at Phase 2) is a monoclonal antibody that binds to **IL-1** itself and is thus a complement to anakinra, which binds to the IL-1 receptor. A similar monoclonal antibody from Novartis (ACZ 885) and one from Eli Lilly are also both at Phase 2. More advanced is tocilizumab (MRA), an anti-**IL-6** receptor monoclonal antibody being developed by Roche and Chugai, which is in Phase 3 trials. In a first Phase 3 trial, this antibody produced striking reductions in symptoms in patients with early-stage disease when injected once every four weeks, proving more effective than conventional DMARDs.

Other monoclonals in development target the cytokines **IL-15** (AMG 714, Amgen, Phase 2), **IFN-α** fontolizumab, Biogen Idec, Phase 2), and **IL-17 (**AIN 457, Novartis, Phase 1), Serono has an **IL-18**-binding protein (tadekinig-alpha) in Phase 2, Synta Pharma has an oral **IL-12** inhibitor (STA-5326, apilimod mesylate, Phase 2) and Kowa is working on an oral inhibitor (K-832) of the production of several cytokines, also at Phase 2.

A large number of compounds are in Phase 2 development that aim to inhibit the cascade of cytokine production and release provoked by TNF-α and IL-1. This is achieved by blocking one of the common signalling pathways following activation of TNF-α and IL-1 receptors on the cell surface. Most of these compounds have been selected to inhibit an enzyme called p38 MAP kinase, which is found in synovial cells in affected joints (Figure 4). Kinase inhibitors are in development by Boehringer Ingelheim (BIBR 796 BS, doramapimod), GlaxoSmithKline (GSK 681323 and 856553), Pfizer (CP-690550 and PH-797804), Roche (R1503), Scios (SCIO-469) and Vertex (VX-702).

Other companies have chosen to target cell adhesion molecules, which influence the infiltration of the synovium and synovial cavity by inflammatory cells. Examples include MLN 3897 (Millennium Pharma) and AVE 9897 from sanofi-aventis at Phase 2 and Millennium's MLN 3701, AVE 1701 (sanofi-aventis) and UCB's CDP 323, all at the Phase 1 stage.

Several other compounds are in development that, like rituximab, target B cells, which play a role in the immune system. These include ocrelizumab (R1594) of Roche (Phase 3) and GSK/Genmab's ofatumumab, Wyeth's TRU-015 and belimumab (LymphoStat-B, Human Genome Sciences), all at Phase 2. T-cell activation may also be important in some cases of RA, and Bristol-Myers Squibb has abatacept (Orencia) that blocks this process. It may provide an alternative to rituximab in those who have not responded adequately to DMARDs and anti-TNF-α inhibitors.

The longer-term future

There are so many processes involved in inflammation and tissue destruction in RA that there are many more compounds under investigation than can be mentioned here. Other types of compounds are being studied by Astellas, AstraZeneca, Dainippon-Sumitomo, Eli Lilly, GW Pharmaceuticals, Pfizer, Serono, Toyama, Wyeth and ZymoGenetics, among others. With such intense research activity, it is likely that the situation of people with RA will be considerably improved over the next decade, with more selective treatments that can slow or stop disease progress and prevent much of the deformity, pain and loss of function that are all too common now.

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Website: www.arthritiscare.org.uk

SCHIZOPHRENIA

What is schizophrenia?

Schizophrenia is a mental illness that affects thinking, perception and behaviour. It is the commonest of a number of diseases called *psychoses*. About a quarter of people with schizophrenia have just one episode, experiencing what are called *positive symptoms*, and then make a good recovery. About two-thirds continue to experience symptoms, with often prolonged intervals of being well. About 10 per cent develop a chronic form of the disease, experiencing severe long-term incapacity, perhaps accompanied by withdrawal, social isolation, flattened mood and poor self-care (*negative symptoms*), but some will eventually recover fully. Approximately 30-40 per cent of people with schizophrenia attempt suicide at some time in their lives.

'POSITIVE' SYMPTOMS OF SCHIZOPHRENIA INCLUDE:

- confused, illogical thinking, poor concentration and speech
- delusions - belief that one is famous, or being persecuted or controlled by others
- hallucinations - hearing voices, seeing visions, smelling or feeling things that are not there

Brain scans during a hallucination show activity in both the visual and auditory areas of the brain (Figure 1). The person experiencing the hallucination is thus not imagining the sights and voices - to them they are real.

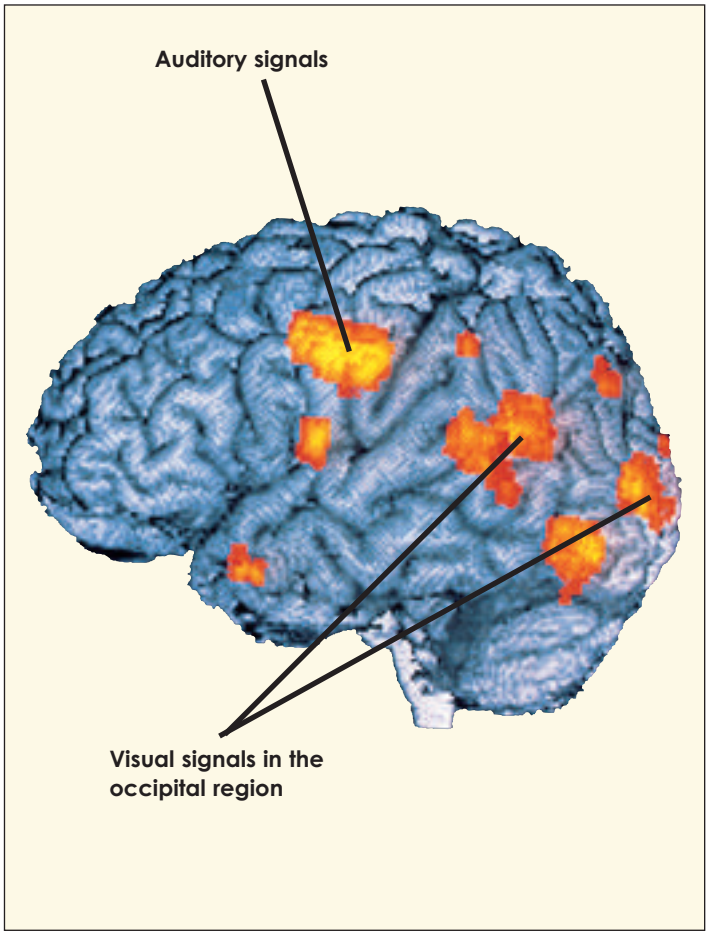

***Figure* 1: Brain activity during an hallucination. Visual and auditory areas of the brain are activated.**

Who does schizophrenia affect and what does it cost?

Schizophrenia affects 1 in 100 people at some point in their lives, with about 250,000 diagnosed cases in Britain at any one time. It is most often diagnosed between the ages of 18 and 30. The chances of developing the illness are higher if a near relative is affected, suggesting a genetic predisposition, but up to 60 per cent of people with schizophrenia have no family history of the illness, so that genetic risks are likely to be only one factor in the disease.

Mental illness places a huge burden on the NHS. In 2003/04, in-patient treatment of mental illness cost £1.3 billion (nearly 10 per cent of all inpatient costs). Schizophrenia and related disorders accounted for over 34,000 in-patient admissions and over 2.24 million hospital bed-days of treatment in that year. It has been estimated that the total cost to society of treating schizophrenia amounted to more than £3.7 billion in 2000.

Present treatments and shortcomings

Early medicines for treating schizophrenia (such as haloperidol and chlorpromazine) are still in use, but have serious side-effects. The worst of these affect a part of the brain called the *extrapyramidal motor tracts*. They range from rigidity and trembling to painful spasms, eye rolling and an inner restlessness called *akathisia*. The development, sometimes months or even years after starting a particular medicine, of uncontrollable facial and bodily movement called *tardive dyskinesia* is especially serious and is often irreversible, even when the medication is stopped. Anti-Parkinson's medications may be given to control these extrapyramidal symptoms.

Established medicines for schizophrenia include several classes of compounds, such as phenothiazines (e.g. chlorpromazine, fluphenazine and trifluoroperazine), butyrophenones (haloperidol and benperidol) and thioxanthenes (flupentixol, zuclopenthixol).

NEW SINCE 2000

2000 - Quetiapine (Seroquel, AstraZeneca)

2003 - Risperidone orodispersable tablets (Risperdal Quicklets, Janssen-Cilag)

2004 - Aripiprazole (Abilify, BMS/Otsuka)

These vary in the pattern and intensity of side-effects they produce (sedation, extrapyramidal symptoms, dry mouth, blurred vision etc) and tolerability varies from patient to patient. Some can be given as injections every two to four weeks, which may aid compliance.

The other principal medications for schizophrenia are the so-called 'atypical' antipsychotic medicines. Clozapine (Clozaril, Novartis) was the first to be introduced, but is now used less often because of the need for continuing blood monitoring. Atypical antipsychotics interact with receptors for neurotransmitters in the brain, including dopamine (DA) and serotonin (5HT), and have improved side-effect profiles, as well as providing good control of positive and negative symptoms. They are, however, more expensive than the older medicines. Other atypicals are risperidone (Risperdal, Janssen-Cilag), olanzapine (Zyprexa, Lilly), quetiapine (Seroquel, AstraZeneca), and amisulpride (Solian, sanofi-aventis). Weight gain is the most common side-effect associated with atypical antipsychotics. It has also been suggested that their use may be associated with a higher incidence of diabetes, although the evidence for this is controversial. However, a need for improved medications remains.

Aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka) works somewhat differently from other atypicals. It is thought to act as a dopamine system stabiliser, through partial agonism, unlike other agents, which mainly act to suppress dopamine.

While medical treatment is important in schizophrenia, psychological therapies can also be of benefit and can be used at the same time. Those most likely to be used in schizophrenia include cognitive behavioural therapy, psychotherapy and family interventions. Unfortunately, access to such therapies under the NHS is currently limited.

What's in the pipeline?

Two modified-release forms of existing atypical antipsychotics are in advanced development. These are Janssen-Cilag's extended-release form of paliperidone, a derivative of risperidone, and AstraZeneca's sustained-release form of quetiapine (Seroquel SR). Other atypicals are mostly taken as twice-daily doses, so these once-a-day formulations should be a useful addition to existing options.

Completely new atypical agents in Phase 3 trial include asenapine (Organon) and bifeprunox, which is being studied by Solvay, Lundbeck and Wyeth, both of which have reached an advanced stage of development. In addition, an existing medicine for epilepsy is also in Phase 3 trial in schizophrenia. Topiramate (Topamax, Janssen-Cilag) is being studied for control of positive symptoms in patients who are resistant to atypicals such as clozapine.

At Phase 2, there are many compounds in clinical trial that act on neurotransmitter receptors in the brain. These include blonanserin (Dainippon-Sumitomo), SB-773812 and SB-223412 (talnetant; both GSK), Org 24448 (farampator; Organon/Cortex), ABT-089 (Abbott), AVE 1625 (sanofi-aventis), idazoxan (Pierre Fabre/Potomac) and SGS518 (Lilly). Also, there are ACP-103 (Acadia Pharma), sabcomeline (Minster Pharma) and ACP-104 (Acadia), SLV313 from Solvay and Wyeth and various other compounds whose exact ways of working may not yet have been fully determined, including lurasidone (Merck Sharp & Dohme /Dainippon-Sumitomo), ocaperidone (Neuro3d), vabicaserin (Wyeth) and others.

This bewildering array of candidate medicines in Phase 2 trials is mirrored at earlier stages too, reflecting the great complexity of brain chemistry and the many possible pathways by which it might be influenced to affect positive and negative symptoms. All of these compounds are being developed in an attempt to find an optimal balance between maximal control of symptoms and the lowest possible incidence of unwanted effects. Companies with a particular engagement in this research include GlaxoSmithKline, Wyeth, Pfizer, Solvay, Lundbeck, sanofi-aventis and others and it must be hoped that their efforts soon result in better treatment options for schizophrenia.

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SLEEP DISORDERS

What are sleep disorders?

Occasional difficulty in sleeping, or in staying awake when desired, is a very common experience and may be considered a normal part of life. However, a prolonged inability to get to sleep or stay asleep (*insomnia*), or a sudden and irresistible urge to fall asleep at inappropriate moments during the day (*narcolepsy*), sufficient to disrupt normal life, are considered to be sleep disorders. They require medical investigation, as do sleepwalking and recurring sudden inability to breathe during sleep (*sleep apnoea*), *Restless legs syndrome* (a feeling of discomfort in the legs when in bed that may be alleviated by moving the legs) is a disorder of the nervous system that commonly results in disturbed sleep.

There are many factors that may contribute to sleep difficulties, including the physical environment (room too hot/too light/too noisy/bed too uncomfortable, etc), medical factors (arthritic or other pain, waking up at night to urinate, side-effects of medication, etc), and psychological influences (anxiety, depression, inter-personal conflict, etc), as well as lifestyle aspects (irregular routines, shift-working, food or drink consumed shortly before bedtime, or in excess, and so on) and these must all be considered and eliminated as possible causes for the sleep disturbance. Nevertheless, it may prove impossible to resolve all sleep difficulties without at least short-term use of medication, and this section considers some of the medicines in use or development for this purpose.

Who do sleep disorders affect?

Insomnia can affect almost anyone. It is estimated that 10-15 per cent of the adult population suffers from chronic insomnia and it is even more frequent later in life. Insomnia is more frequent among those with obesity, high blood pressure, congestive heart failure and anxiety or depression. In an Australian survey of people over

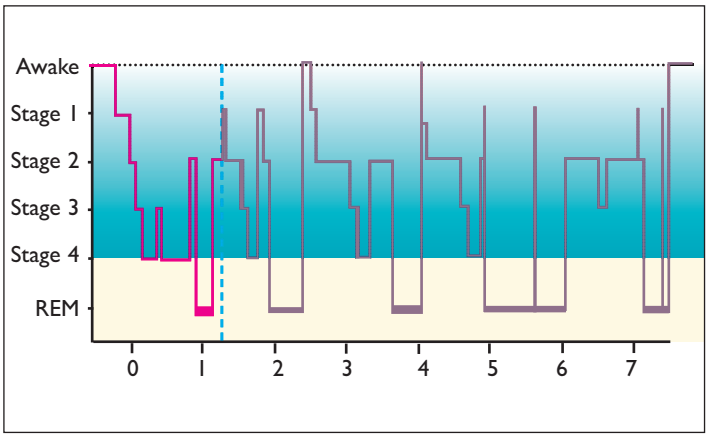

***Figure 4*: Normal sleep progresses in successive cycles of approximately 90 minutes, passing from light (stages 1 and 2) to deep (stages 3 and 4) sleep and then into rapid-eye-movement (REM) or dreaming sleep. As the night progresses, the amount of time spent in deep sleep tends to decrease and the duration of REM sleep tends to increase.**

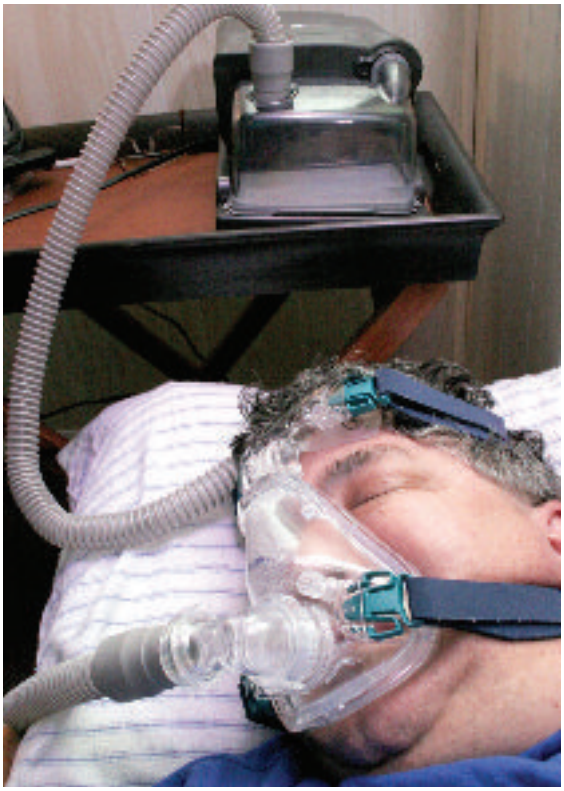

***Figure 2*: A continuous positive airway pressure (CPAP) machine keeps the airways open in a person with sleep apnoea, allowing uninterrupted sleep.**

60, those reporting sleep difficulties were more than three times more likely to be depressed than those without such difficulties and similar data have been reported from other countries.

Narcolepsy is estimated to affect about 1 in 2,000 people in the UK, but only about 2,500-3,000 have been diagnosed and are being treated. It is a life-long condition.

Sleep apnoea is most likely to affect people who are overweight or obese, and the risk increases with age. In a population survey in the United States, a quarter of those interviewed were judged to have a high risk of sleep apnoea, including 57 per cent of obese individuals. Like obesity, sleep apnoea has been associated with a raised risk of developing diabetes.

Restless legs syndrome has been reported to affect between 3-9 per cent of adults in the general population. It becomes more common with age and affects women more often than men. It has been reported to be more common among people with type 2 diabetes.

Present treatments and shortcomings

Historically, insomnia which was not controlled by improving sleeping habits and other non-medical measures was most often treated with barbiturates or benzodiazepine tranquillisers. The barbiturates are controlled drugs and have fallen from favour because of their potential for the development of tolerance and dependence and the dangers of overdose. Benzodiazepines also have a potential for addiction, but are considered acceptably safe for short-term use. Short-acting types may be preferred, as they are

less likely to cause drowsiness during the day. 'Rebound insomnia' may occur on discontinuing benzodiazepines, especially if they have been used for an extended period.

More recently, three hypnotic (sleep-inducing) medicines have been introduced for insomnia that have a different chemical structure from benzodiazepines. These are zaleplon (Sonata, Wyeth), zolpidem (Stilnoct, sanofi-aventis) and zopiclone (Zimovane, sanofi-aventis). These medicines were developed to be less likely to induce tolerance and dependence than benzodiazepines, but they act partly through the same receptors in the brain, which act on the neurotransmitter gamma-amino butyric acid (GABA), and are also recommended only to be used in the short term.

Only one medication is available for the treatment of the excessive daytime sleepiness associated with narcolepsy and with obstructive sleep apnoea. This is modafinil (Provigil, Cephalon). How it works is not precisely known, but it acts as a central stimulant to promote wakefulness. Obstructive sleep apnoea is otherwise most often treated mechanically, using a continuous positive air-pressure (CPAP) pump and face-mask at night, to keep the airways open during sleep.

Medicines acting on the neurotransmitter dopamine play a central role in the treatment of restless legs syndrome. Two are available for use in the UK: pramipexole (Mirapexin, Boehringer Ingelheim) and the more recently introduced ropinirole (Adartrel, GlaxoSmithKline). Nausea and other gastrointestinal symptoms, sleepiness and uncontrolled movements may occur as side-effects with these medicines.

What's in the development pipeline?

Additional compounds acting on GABA receptors are in development for treating insomnia. Neurocrine Biosciences has a new non-benzodiazepine agent (Indiplon) in Phase 3 trial that acts on GABA receptors believed to be responsible for promoting sleep. It is being aimed first at insomnia resulting from difficulty with getting to sleep. Gaboxadol (Merck Sharp & Dohme /Lundbeck), which is also in Phase 3 trial, appears to interact directly with GABA receptors different from those on which benzodiazepines act. It increases the amount of slow-wave (deep) sleep without affecting REM-sleep. Two other GABA-receptor agents are in Phase 2 trials: Evotec's EVT-201 and the partial agonist, Neurogen's NG2-73.

Several compounds are under investigation that interact with serotonin receptors instead of GABA receptors. These include eplivanserin (Phase 3) and volinanserin (M-100907, Phase 2) from sanofi-aventis, Organon's Org 50081 (Phase 3), Lilly's pruvanserin (Phase 2), Acadia's ACP-103 and Arena's ADP125, both in Phase 2 trials. These offer the prospect of increased slow-wave sleep and improved treatment of sleep maintenance, i.e. fewer awakenings and more rapid return to sleep after awakening.

Perhaps the greatest excitement in the treatment of insomnia revolves around new compounds that act on melatonin receptors. Melatonin is a naturally occurring hormone that has long been known to be important for circadian rhythms and the sleep-wake cycle and receptors in the brain are known to regulate these circadian rhythms. Takeda has developed a new agent, ramelteon (Rozerem) that acts selectively on these receptors, which is in Phase 3 trials in Europe. Results from studies showed that ramelteon reduced the time it took to fall asleep and its use was not associated with rebound insomnia or withdrawal symptoms on stopping treatment.

Two other new agents that act on this system are also in Phase 3 trials. Alliance Pharmaceuticals has synthetic melatonin (Posidorm) under study in elderly patients with insomnia and in those with shiftwork-associated sleep disorder and Vanda is studying VEC-162 in transient insomnia. Another melatonin analogue being studied in elderly patients is Phase2 Discovery's PD-6735, which is in Phase 2 trial.

New treatments are also being explored for restless legs syndrome. Schwarz Pharma has a skin patch form of rotigotine (Neupro), which is already indicated for use in Parkinson's disease, in Phase 3 trial and Newron Pharmaceuticals is developing safinamide, which has reached Phase 2. It is also in development for treating Parkinson's disease. Lastly, XenoPort has reported encouraging results from its Phase 2 trials of XP13512, a derivative of gabapentin (Neurontin, Pfizer) which has long been used to treat epilepsy, and XP13512 is now in Phase 3 development in restless legs syndrome by XenoPort's partner GlaxoSmithKline.

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STROKE

What is stroke?

A stroke is sudden damage to blood vessels in the brain that causes symptoms lasting for more than 24 hours (most usually paralysis affecting one side of the body and/or speech difficulties). If such an event clears up spontaneously within less than 24 hours, it is termed a **transient ischaemic attack** (TIA). The majority of strokes in Western countries (about 85 per cent) are ischaemic strokes, which result from arterial blockage by a blood clot (Figure 1) or detached plaque from elsewhere in the circulation (see *Atherosclerosis*). Most of the rest are a result of brain **haemorrhage** (bleeding from a ruptured blood vessel into the brain), and in this type of stroke there may be severe headache and vomiting, as well as paralysis and speech difficulties.

Brain damage in stroke is caused by a reduction in the oxygen supply to the brain and chemical changes resulting from it. The brain consumes oxygen at a high rate, but has no oxygen reserve. Hence, it is entirely dependent on a continuous blood supply through the carotid and vertebral arteries.

There is a more insidious side to strokes. Many people experience a series of mild ischaemic strokes over a period of years. These may be unnoticed - *silent ischaemia* - or cause transient symptoms, but over time the accumulated damage is responsible for about 25 per cent of cases of senile dementia.

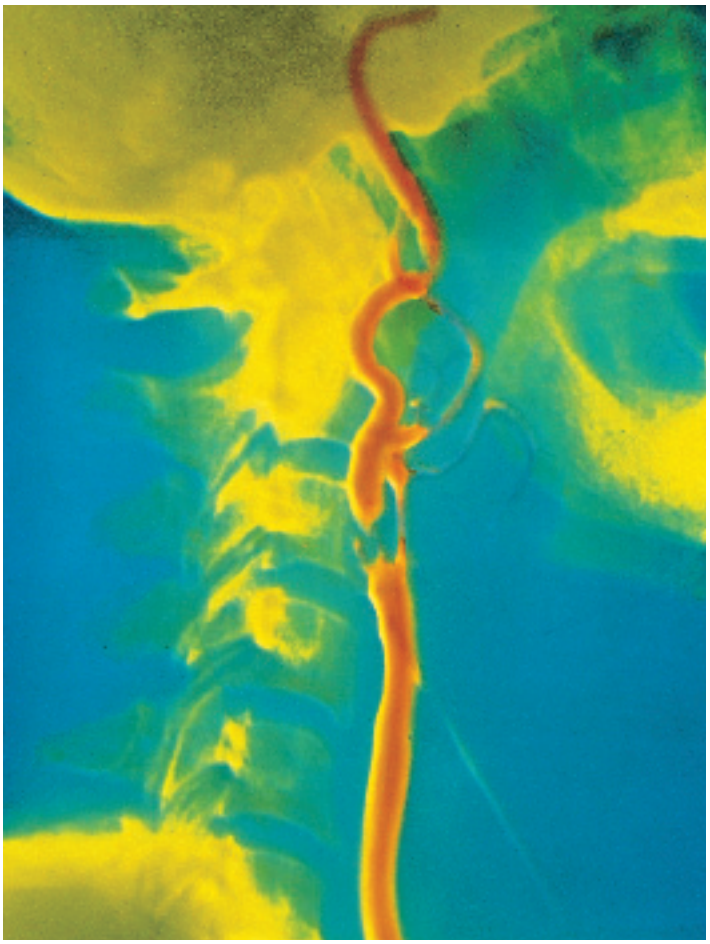


***Figure* 1: Blockage in the carotid artery leading to the brain**

Who does stroke affect and what does it cost?

More than 130,000 people a year suffer a stroke in England and Wales and 60,000 die of cerebrovascular disease, making stroke the third most common cause of death, after heart disease and cancer. Between 15-20 per cent of people experiencing a stroke die within a month. Of those that survive, some do not regain the full use of their faculties. More than 300,000 people in the UK are believed to live with moderate to severe disability as a result of a stroke.

Although stroke can affect younger people, it is largely a disease of older age (Figure 2) and 85 per cent of strokes are in the over-65s. It is well recognised that there are risk factors for stroke apart from age. The clearest is high blood pressure (see *Hypertension*), while smoking, heavy drinking and diabetes also play a part.

Strokes are estimated to have cost the NHS over £2.8 billion in direct costs in 2004, being responsible for over 2.6 million bed-days of hospital care in 2003/04. In addition, informal care costs have been estimated at £2.4 billion and indirect costs due to loss of income and disability benefit payments at £1.8 billion, giving a total cost to society of £7 billion year due to strokes.

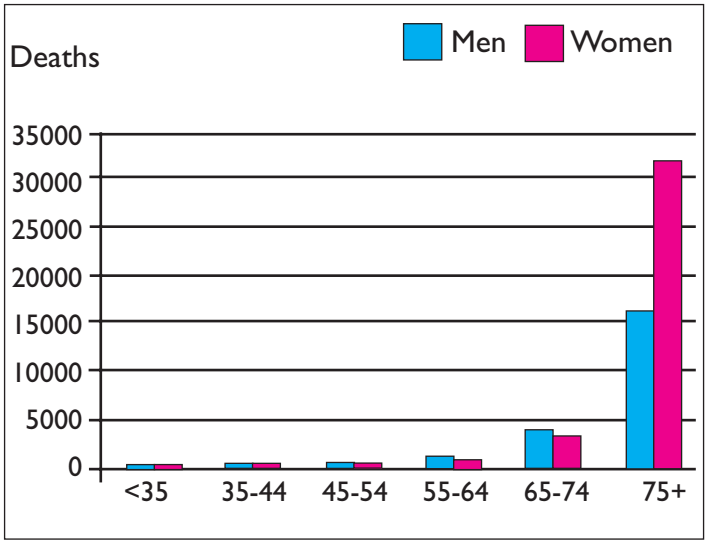
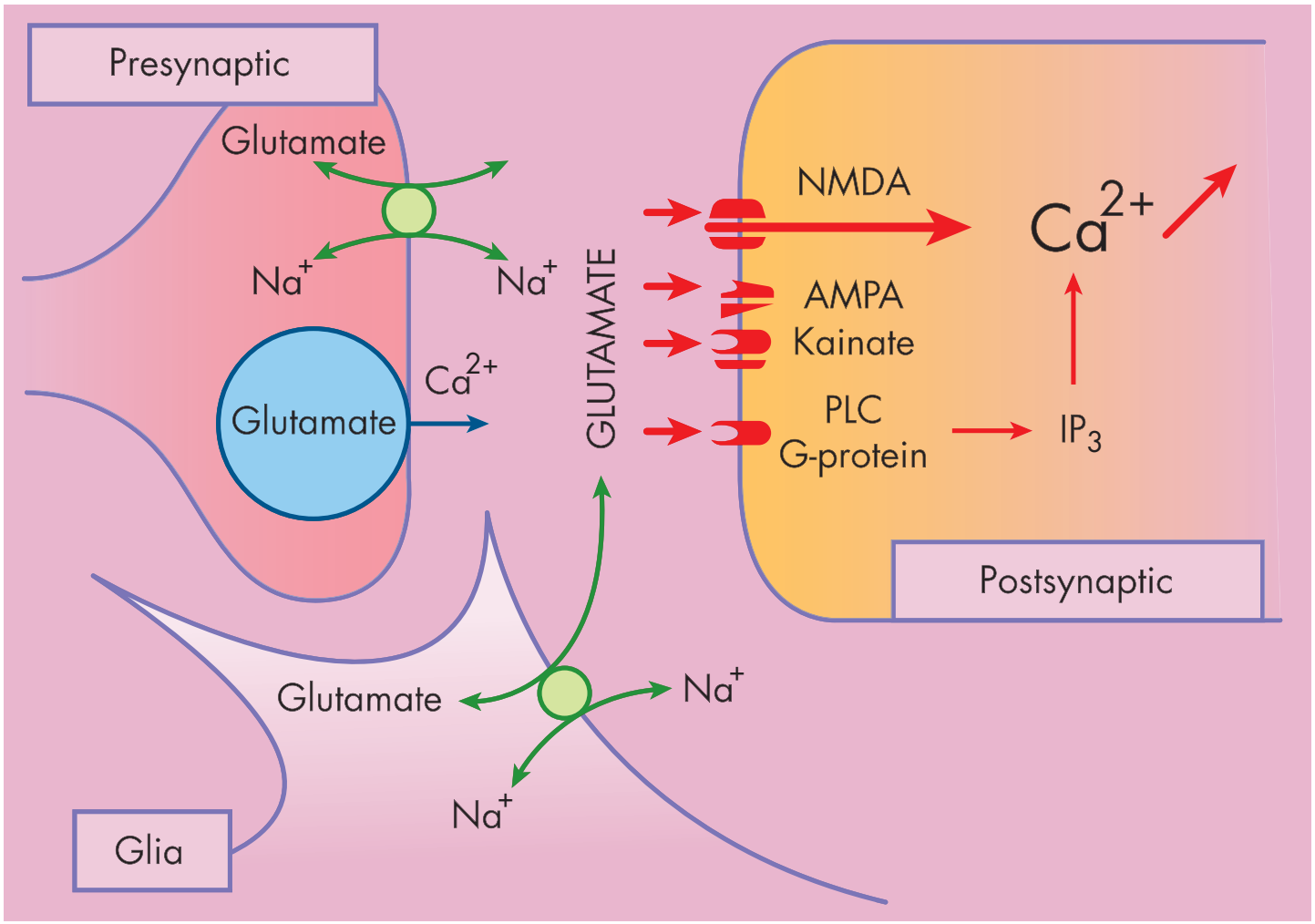


***Figure* 2: Age distribution of deaths from stroke in the United Kingdom in 2004**
Source: British Heart Foundation Statistics Database

Figure 2: **The "glutamate cascade" in ischaemic damage. Glutamate-driven influx of Ca^{2+} ions involving NMDA and AMPA receptors leads to postsynaptic cell death.**

Key: PLC = phospholipase C; IP3 = inositol triphosphate



Present treatments and shortcomings

Medical treatment for stroke has two different objectives:

- emergency treatment to limit damage in the hours and days following an acute stroke
- prevention of a first or subsequent stroke (over a long period).

Emergency treatment is complicated by the fact that there are two different causes of stroke (clots and haemorrhage), which may be difficult to distinguish in the initial clinical examination. Brain scanning by computed tomography or magnetic resonance imaging is needed to distinguish between these, but is not always available. A therapy suitable for a clot-induced stroke (for example, clot-busting and 'blood thinning' medicines) would be potentially harmful in a haemorrhagic stroke, as it might make the bleeding worse and cause even greater brain damage. For this reason, medicines (heparins and fibrinolytics such as streptokinase and urokinase) that are available for use in heart attack, deep vein thrombosis and post-operative prevention (see *Ischaemic Heart Disease* and *Thrombosis*) are generally not indicated for use in stroke in the UK. Only one, the 'clot-buster' enzyme alteplase (Actilyse, Boehringer Ingelheim), is currently available for acute management of stroke, and this may only be used where haemorrhagic stroke has been ruled out by brain imaging.

Prevention of stroke includes both minimising risk factors, for example by treating high blood pressure, and the long-term use of medication that can prevent the development of ischaemic stroke. Daily low-dose aspirin reduces platelet stickiness and decreases the risk of recurrent stroke by about 15 per cent. Clopidogrel (Plavix, sanofi-aventis and BMS) and dipyridamole (Persantin Retard, Boehringer Ingelheim) are other anti-platelet agents also available for this purpose. Anti-platelet medicines are not used in those who have had a haemorrhagic stroke.

Some antihypertensives, such as ACE-inhibitors and angiotensin receptor blockers, have been shown to prevent heart attacks and stroke in those with established cardiovascular disease. Statins have also been shown to reduce the risk of stroke, but have not been explicitly indicated for this purpose. Atrial fibrillation (see *Cardiac Arrhythmia*) carries a high risk of stroke, and many people with this condition will be given anticoagulation treatment with warfarin to minimise this risk.

What's in the development pipeline?

Emergency treatment of ischaemic stroke seeks to restore circulation to affected brain areas as far as possible, to limit the extent of nerve cell death, and thus preserve brain function. Several companies have projects to develop alternative **clot-digesting agents**. At Phase 3, these include ImaRx Therapeutics's PROLYSE, ancrod (Viprinex, Neurobiological Technologies), which is derived from Malaysian viper venom, and desmoteplase (Paion/Lundbeck/Forest Labs), based on a protein originally isolated from the saliva of vampire bats. At the Phase 2 stage is V10153 (Vernalis), which is expected to both dissolve an existing clot and prevent new clots from forming.

Brain cell stress in acute stroke results from oxygen and energy deprivation. It is thought to lead to accumulation of the neurotransmitter glutamate and a massive influx of sodium and calcium ions into neuronal cells. This leads to activation of calcium-dependent enzymes, the generation of damaging reactive molecules such as free radicals, and the initiation of programmed cell death (apoptosis). Many attempts have been made to stop this toxic 'glutamate cascade' by treatment with neuroprotectants that act on one or other step in the process. However, although this has been achieved in animal models, human trials have so far largely failed to show clinical benefit, perhaps partly because of inevitable delays in starting treatment (more than three hours after the event), by which time damage may be irreversible.

Despite earlier disappointments, several companies have potential medicines to protect nerve cells in development. At Phase 2, D Pharm has the calcium-binding compound DP-b99 and Paion is working on enecadin, a blocker of sodium and calcium channels. Taking a different approach are Daiichi-Sankyo, which has piclozotan in Phase 2 trial, and Ono and Merck Sharp & Dohme, who are investigating a compound (ONO-2506) that modulates the activity of astrocytes - cells which surround and support nerve cells in the brain. Ono is also conducting a Phase 1 study of ONO-2231 for this indication.

Stroke prevention is also still a focus of development, particularly in the context of **atrial fibrillation**. The most advanced projects here are dabigatran etexilate (RENDIX, Boehringer Ingelheim), idraparinux (sanofi-aventis) and a modified form of idraparinux (SSR 126517, sanofi-aventis), which are all in Phase 3 trial. Bayer has BAY 59-7939 (rivaroxaban) in Phase 2 trial and Solvay is studying SB 424323 (odiparcil) at the same stage. GSK also has GSK 813893 in a Phase 1 study and Trigen has TGN 167 at this stage.

Further trials of anti-platelet medicines for stroke prevention are also continuing. Boehringer Ingelheim is comparing the combination of extended-release dipyramidole plus aspirin

***Figure 2*: Once the immediate post-stroke period is passed, physiotherapy is of vital importance for regaining function as far as possible.**

(Asasantin Retard) with clopidogrel (Plavix, sanofi-aventis). The study will also test whether addition of the angiotensin receptor blocker telmisartan (Micardis) can further reduce stroke risk in patients who have already had one stroke. In a different setting, Eli Lilly is testing the ability of the anti-platelet agent prasugrel to prevent strokes in people with acute coronary syndrome (heart attack or unstable angina) undergoing angioplasty.

Lastly, there are new developments too in treating haemorrhagic stroke. Novo Nordisk is running a Phase 3 trial of its NovoSeven, which has shown evidence in earlier Phase 2 trials of an ability to limit the extent of bleeding into the brain if administered within three hours of stroke onset. Evidence of a reduction in post-stroke disability in this setting would be a very welcome step forward.

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THROMBOSIS

What is thrombosis?

A thrombosis is a clot inside a blood vessel which restricts or blocks blood flow. Maintaining the liquid state of the blood depends on complex interactions between blood cells, the cells lining the blood vessels and substances in the blood itself. These promote coagulation when required, but prevent it at other times. For example, injury, exposure to air and to collagen fibres at the site of damage initiates the clotting process. Collagen is a fibrous protein and a major component of cartilage, bone and connective tissue. Blood platelets become sticky and aggregate and a network of fibrin fibres forms which binds the clot together (Figure 1), stopping bleeding.

In some disease states, this balance fails and clots develop inside arteries. This may result in a heart attack or stroke (see *Ischaemic Heart Disease* and *Stroke*). If a clot forms in a vein (*venous thromboembolism, VTE*) deep in the tissues, the obstruction to blood flow can cause painful ischaemia and may have serious long-term consequences. There is also a risk that part of it may detach and travel to the heart, brain, or lungs, where it can cause a heart attack, stroke or pulmonary embolism. Clot formation in a major vein (*deep vein thrombosis, DVT*) after operations such as hip or knee surgery, or through prolonged immobility, such as during long-distance air travel, can put life at risk. A clot in a superficial vein causes inflammation, known as phlebitis, but carries less risk of detachment and, with rest, normally settles down quickly. Clot and plaque formation (see *Atherosclerosis*) are both made more likely by risk factors such as smoking, high cholesterol, high blood pressure and diabetes (see *Hypertension* and *Diabetes*).

Who does thrombosis affect?

It has been estimated that venous thromboembolism causes around 32,000 deaths each year in the UK. Pulmonary embolism following deep vein thrombosis is the immediate cause of death in 10 per cent of all patients who die in hospital. The total cost of managing venous thromboembolism in the UK was estimated in 2005 at approximately £640 million.

Present treatments and shortcomings

From a medical point of view, there are two separate, though overlapping, issues. The first is the prevention of blood clots. This may be a temporary requirement after an operation or accident, or it may be part of long-term management after a first heart attack or other problems with the circulation. The second is the removal or reduction of clots once they have formed. These situations present different challenges and require different medicines (Figure 2).

Thrombosis **prevention** involves the use of either anti-platelet agents, or anti-coagulants that inhibit components of the process that produces the fibrin tangles in clots. The best-known anti-platelet medicine is aspirin, which decreases platelet stickiness and markedly reduces the risk of a heart attack or stroke in those who have already had one, or who have unstable angina (see *Ischaemic Heart Disease*). Dipyridamole (Persantin, Boehringer Ingelheim) is also used for this purpose, alone or in combination with aspirin. A more recently introduced oral anti-platelet medicine is clopidogrel (Plavix, sanofi-aventis/BMS), which prevents clumping of blood cells.

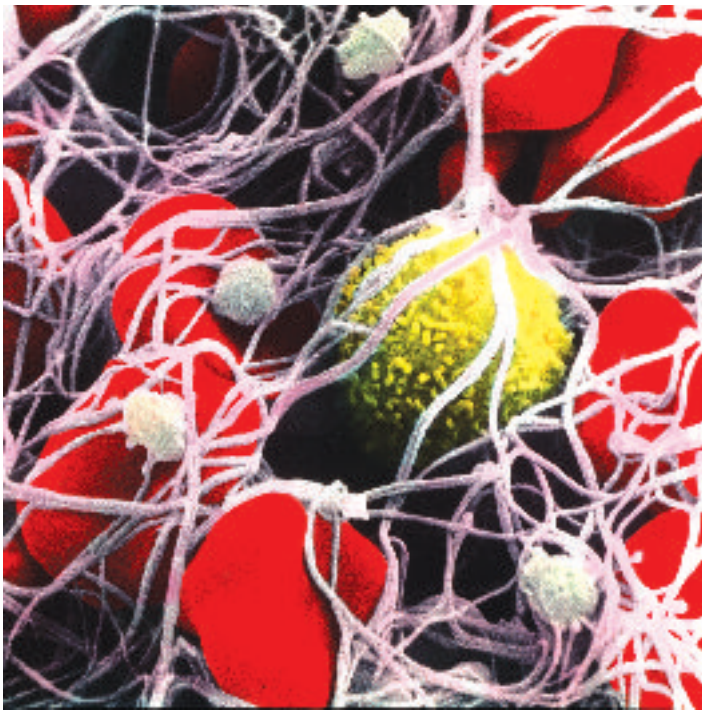

***Figure* 1: Scanning electron micrograph of a blood clot, showing fibrin tangles, trapped red blood cells, small platelets and a white blood cell.**

Heparin and heparin derivatives such as dalteparin (Fragmin, Pfizer), enoxaparin (Clexane, sanofi-aventis), tinzaparin (Innohep, Leo) and bemiparin (Zibor, Amdipharm) are the main medicines used for short-term prevention of blood clotting in the hours immediately following a heart attack or stroke, and during operations such as angioplasty. Also used in acute heart problems are Integrilin (GlaxoSmithKline), Aggrastat (Merck Sharp & Dohme) and the monoclonal antibody abciximab (ReoPro, Lilly). They are normally given under specialist care by injection, in addition to aspirin and heparin. Also used for prevention of venous thromboembolism during surgery, as well as for treatment of deep vein thrombosis and pulmonary embolism, is fondaparinux (Arixtra, GlaxoSmithKline).

NEW SINCE 2000

2000 - Tenecteplase (Metalyse, Boehringer Ingelheim)

2002 - Fondaparinux (Arixtra, GSK)

The **treatment** of clots that have already formed is mainly with so-called clot-busting medications such as Streptase from ZLB Behring, or alteplase (Actilyse, Boehringer Ingelheim), tenecteplase (Metalyse, Boehringer Ingelheim) and reteplase (Rapilysin, Roche). These medicines must all be given by injection under expert supervision and within three to six hours of suspected heart attack if they are to be of benefit. Fondaparinux or heparins such as enoxaparin and dalteparin are also indicated for the treatment of clots in pulmonary embolism and deep vein thrombosis. Bleeding and depressed platelet counts are side-effects associated with heparins and careful monitoring may be required to avoid overdosing.

What's in the development pipeline?

A considerable number of new compounds are in development for the **prevention of venous thromboembolism** Many of these are *inhibitors of activated Factor X*. At Phase 3, Bayer has oral rivaroxaban (BAY 59-7939) in trial for prevention of VTE after surgery. Another orally administered agent at Phase 3 is the capsule formulation of heparin being developed by Emisphere Technologies. Sanofi-aventis is also studying enoxaparin for use in VTE prevention in interventions such as angioplasty.

There are further agents for VTE prevention in Phase 2 trials. Astellas has YM-150 under study for post-surgery prevention and Lilly is developing LY517717 for the same purpose. Schering-Plough's SCH 530348 and sanofi-aventis's SR 123781 and AVE 5026 are also in Phase 2 study for VTE prevention.

At Phase 1, new compounds include Inspire Pharma's anti-platelet agent INS50589, EMD 503982 (Merck Pharmaceuticals) and AVE 3247 (sanofi-aventis) and TGN 167 and TGN 255, being developed by Trigen Holdings.

The other main category of new agents under development for VTE prevention are *thrombin inhibitors*. The furthest advanced is dabigatran (Rendix, Boehringer Ingelheim), which is in Phase 3 study. Other thrombin inhibitors at Phase 2 are AZD 0837 (AstraZeneca), MCC-977 (Mitsubishi Pharma) and PD-348292 (Pfizer).

New compounds are also under development for **VTE treatment**. These include both Factor Xa inhibitors and thrombolytic enzymes. Amongst the first group, sanofi-aventis is developing idraparinux

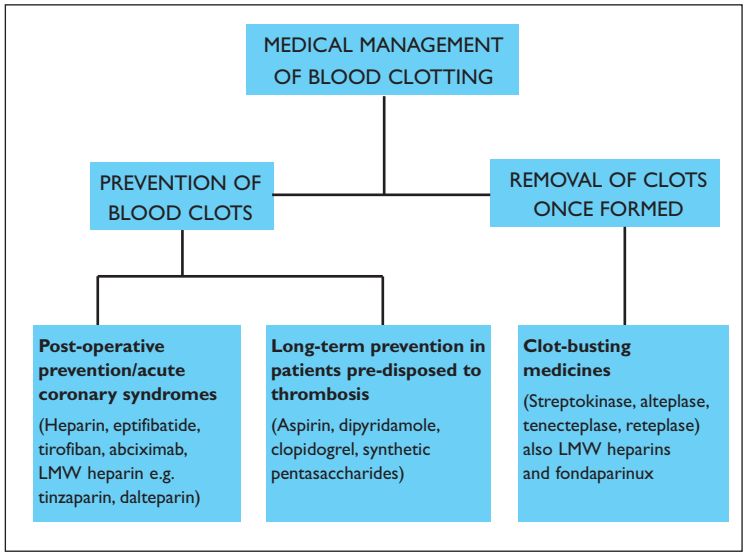

***Figure 2*: Once the immediate post-stroke period is passed, physiotherapy is of vital importance for regaining function as far as possible.**

for the long-term treatment of deep vein thrombosis (Phase 3). This long-acting compound only needs to be injected once a week, unlike most other medicines in this class. Meanwhile, Bristol-Myers Squibb has two direct Factor Xa inhibitors in Phase 2 trial: BMS-562247 (apixaban) and DPC-906 (razaxaban).

New thrombolytics are also under development. Menarini has amediplase in Phase 3 trial for thrombolysis in acute MI, and this may also have uses in other situations such as pulmonary embolism.

A number of other quite different approaches to thrombosis management are also being explored. For example, AstraZeneca's AZD 6140 is in Phase 3 trial in acute coronary syndrome, while Eisai is studying E-5555 in Phase 2 trial for the same condition and Daiichi-Sankyo has DZ-697b in Phase 1 trial. Thus, it is clear that there is still major research and development effort going into developing better thrombosis treatments.

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TRANSPLANTATION

What is transplantation?

Solid organ transplantation is the use of a donor organ to replace a diseased or damaged one. Transplantation can range from a relatively minor procedure, such as the graft of a cornea in the eye, up to complex operations to replace the heart and lungs or liver. Life-long suppression of the recipient's immune system is usually necessary to prevent rejection of the grafted tissue.

Bone marrow transplantation is a similar procedure in which the tissue transplanted is not solid, but is instead a suspension of bone marrow or blood stem cells that can repopulate the recipient's empty bone marrow spaces and recreate a functioning immune system. This may be done to permit the use of intensive chemotherapy to completely eliminate malignant cells, as in certain leukaemias. When the donor bone marrow comes from another individual - *allogeneic* bone marrow transplantation - life-long immunosuppression is required to prevent the newly transferred immune cells from destroying recipient organs, a reaction known as graft versus host disease (GVHD). Immunosuppression is not required if the bone marrow cells are taken from an individual and re-infused after chemotherapy - *autologous* bone marrow transplantation.

Who needs transplants?

Solid organ transplantation is a last-resort treatment aimed at preserving an acceptable quality of life when medical and other treatment has failed. When an organ such as the heart, liver or kidney, has suffered such damage that it can no longer function, or has to have its function replaced by a procedure such as dialysis in the case of the kidney, transplantation of a donor organ may be considered.

In addition to solid-organ transplants, there were 2,320 first blood and bone marrow transplants (841 allogeneic and 1,479 autologous) performed in the UK in 2004, the great majority for cancers such as leukaemia or lymphoma (see *Leukaemia*). More than 80 per cent of these transplants were of blood stem cells.

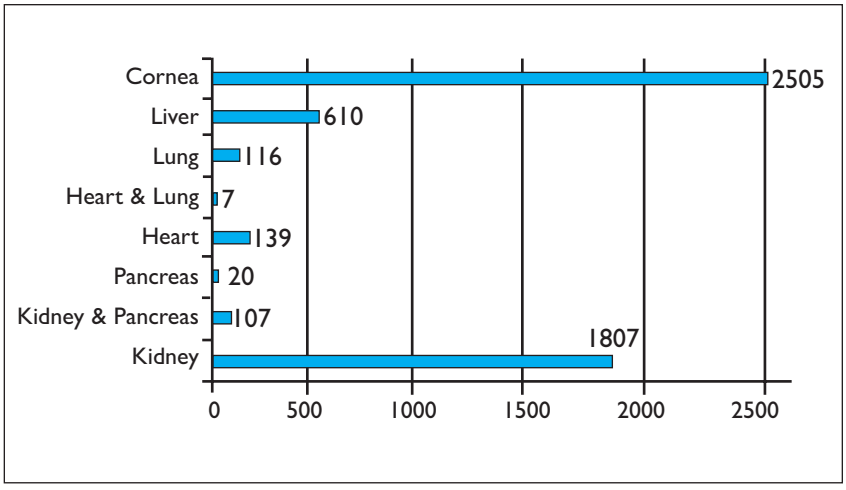

***Figure* 1: Solid organ transplants in the United Kingdom in 2005/06.**
Adapted from: NHS Transplant Activity Report 2005/06.

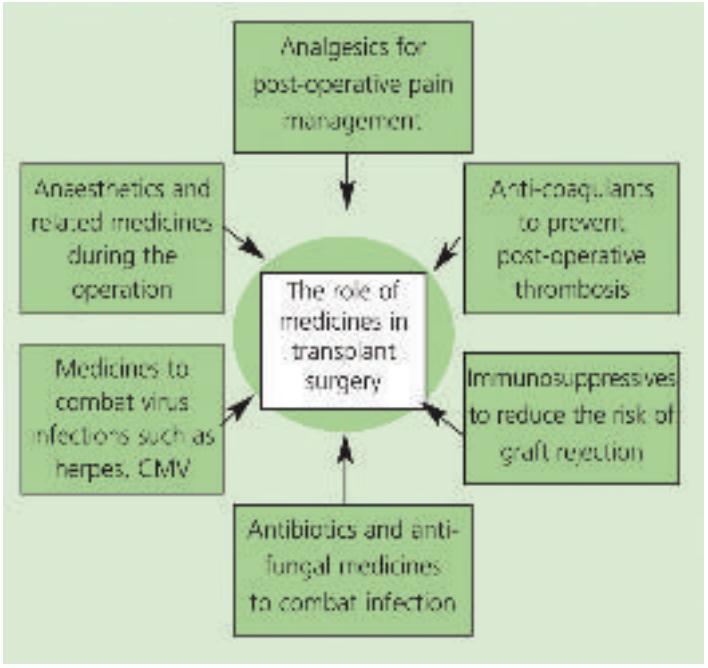

***Figure* 2: Some of the many types of medicine used in transplant surgery**

The first successful kidney transplant took place over 50 years ago. Today, the graft survival rate five years after transplant is typically over 75 per cent for a kidney taken from a dead person and over 85 per cent for one from a living matched donor. Heart transplants are also undertaken, although less frequently, because of the shortage of donor organs. The five-year patient survival rate is about 70 per cent. Other organs transplanted are the liver (first achieved in 1967, five-year graft survival rate about 65-70 per cent) and, less commonly, the pancreas (one-year survival rate about 80 per cent for kidney + pancreas transplants).

Current practice and shortcomings

The major success of transplant surgery over the past 30 years would not have been possible without a battery of medicines (Figure 2). Most of these are discussed in other sections (see *Pain, Thrombosis, Fungal Infections, Bacterial Infections, Herpes*), but immunosuppressive agents, essential to prevent graft rejection, are discussed here.

The earliest medicines used to suppress rejection, such as azathioprine and 6-mercaptopurine, are somewhat toxic when used alone and they now have only a supporting role to play. A major breakthrough was the discovery of a molecule called cyclosporin A (Sandimmun, Novartis) which is able to prevent the body's immune system from attacking the graft. Another key event was the introduction in around 1970 of tissue matching. Together, these two developments greatly enhanced success rates in transplantation.
Cyclosporin has a fine line between working effectively and damaging the body. The original injected form

NEW SINCE 2000

2001 - Sirolimus (Rapamune, Wyeth)

2002 - Mycophenolate mofetil (CellCept, Roche)

2003 - Daclizumab (Zenapax, Roche)

2003 - Valganciclovir (Valcyte, Roche)

2004 - Mycophenolate EC (Myfortic, Novartis)

(Sandimmun) also had an unpredictable absorption that made it necessary to monitor blood levels carefully, although the more recently introduced oral form (Neoral) gives more predictable blood levels. Cyclosporin is used together with prednisone and/or azathioprine to prevent acute rejection and for the prevention and treatment of GVHD. Specialist transplant centres often develop their own standard procedures for the use of such combinations, with larger centres that carry out more transplants often achieving better results than smaller centres.

Other immunosuppressants have been made available since the introduction of cyclosporin. Tacrolimus (Prograf, Astellas) is used in kidney, heart and liver transplants and the more recently launched sirolimus (Rapamune, Wyeth) is used in kidney transplantation. A fourth immunosuppressant, mycophenolate (Cellcept, Roche and the enteric-coated, delayed release form Myfortic, Novartis) is only for use in combination with cyclosporin and corticosteroids. Cyclosporin and tacrolimus block the activation of cells that attack the transplanted tissue and lead to graft rejection. Both are potentially damaging to the kidneys and may induce high blood pressure. Sirolimus does not show the same damage to the kidneys as cyclosporin and tacrolimus; however, it may also cause high blood pressure and raises blood triglyceride and cholesterol levels.

Two monoclonal antibodies have been made available for use together with immunosuppressive therapy in kidney transplantation. These are basiliximab (Simulect, Novartis) and daclizumab (Zenapax, Roche). They target a receptor for interleukin-2 which plays a key role in the rejection process. Both reduce rejection, reducing the need for steroids and the risk of infection.

What's in the development pipeline?

Everolimus (Certican, Novartis) is an immunosuppressant belonging to the same family as sirolimus. In Phase 3 trials, used with reduced-dose oral cyclosporin, steroids and basiliximab,

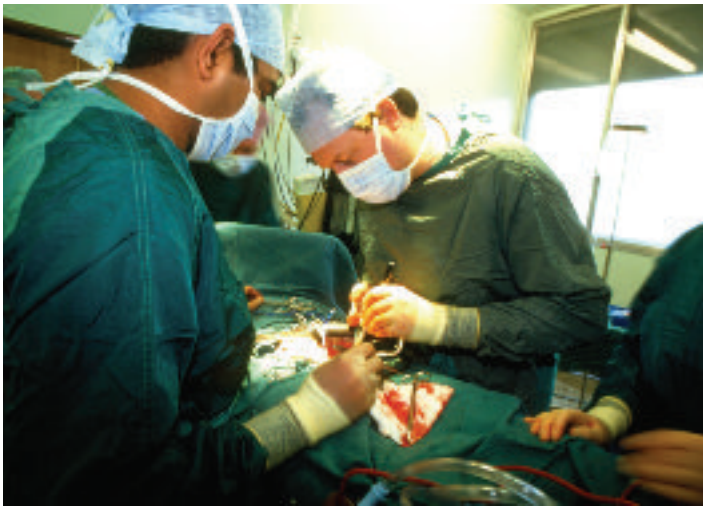

***Figure* 3: Surgeons performing a kidney transplant. Kidney is the most commonly transplanted organ and the operation has a high success rate.**

everolimus has been found to be associated with acute graft rejection rates as low as 3.5 per cent at 6 months and reduced signs of kidney damage, as well as a low rate of infection with cytomegalovirus - a common problem in transplantation. Also at an advanced stage is a modified release form of tacrolimus.

Bristol-Myers Squibb is studying belatacept in Phase 3 trial for the prevention of kidney graft rejection. Also at Phase 3, Wyeth is continuing to develop sirolimus in kidney transplantation and for liver transplantation.

Pfizer has a completely new type of immunosuppressant in Phase 2 trial for kidney transplantation. Its CP-690,550 is an inhibitor of an enzyme that plays a key role in the development and function of T cells. Inhibiting this enzyme selectively should result in effective immunosuppression with fewer side-effects than seen with less targeted agents. Novartis is also investigating a compound (AEB071) that targets T cells and this is also in Phase 2 trial. Roche and BioCryst are collaborating to develop BCX-4208, another T cell targeted agent which is in Phase 1 trials.

Also at Phase 2 are ISA247 (Isotechnika), an immunosuppressant of the same type as cyclosporin which is also being investigated as a possible treatment for psoriasis, and the antiviral compound maribavir (Viropharma), to inhibit cytomegalovirus. This latter compound has shown encouraging preliminary results in a trial in stem cell transplantation.

The development of new and more selective immunosuppressants offers hope of a better future for those undergoing transplantation. However, its must not be forgotten that the main limitation today is the lack of availability of donor organs, which results in many patients dying before they can be given a transplant and efforts to address this problem are urgently needed.

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TRANSPLANT SUPPORT NETWORK,
The Temple Row Centre, 23 Temple Row, Keighley, BD21 2AH.
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Website: www.transplantsupportnetwork.org.uk

OR

BRITISH ORGAN DONOR SOCIETY (BODY) ,
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Website: www.bodyuk.org

TUBERCULOSIS

What is tuberculosis?

Tuberculosis (TB) is a bacterial infection caused by *Mycobacterium tuberculosis* or, occasionally, by one of two other related bacteria. It most often affects the lungs (pulmonary TB) but can also affect the central nervous system, lymphatic and genitourinary systems, circulation, and bones and joints. It is highly infectious and is spread from one person to another by the inhalation of airborne droplets containing the bacteria expelled by coughing or sneezing. About 90 per cent of those infected do not show any symptoms but remain carriers of the disease (*latent* TB). Of these, around 10 per cent will develop an active infection at some point in their lives. Conversion from latent to active disease is more likely in those whose immune system is depressed, such as those infected with HIV, and in people treated with medicines that block TNF-α, which is important in the body's immune defence against TB.

Active TB is characterised by symptoms such as a cough, chest pain and the coughing up of blood in those with pulmonary TB and by fever, chills, night sweats, appetite and weight loss and fatigue in those with systemic disease. The WHO has estimated that people with active TB will infect on average 10-15 people a year and, untreated, about half of those will eventually die of TB.

Who does tuberculosis affect?

The World Health Organisation estimates that around one-third of the world's population (about 2 billion people) carry the TB bacterium and that about 8 million develop the disease each year, of whom roughly 1.6 million die. Of the active cases of TB, over 1.5 million a year occur in sub-Saharan Africa and nearly 3 million in Southeast Asia. TB was diagnosed in more than 8,000 people in the UK in 2005, and this figure is growing year by year. Nearly 3,500 cases were recorded in London alone. Almost three-quarters of those developing active TB in the UK are born in countries where it is endemic.

Present treatments and shortcomings

Recommendations for treatment of TB are contained in a guideline published by the National Institute for Health and Clinical Excellence (NICE) in March 2006. Standard treatment for active pulmonary TB consists of a six-month period of treatment with isoniazid + rifampicin, supplemented during the first two months with pyrazinamide and ethambutol. Fixed combinations such as rifampicin + isoniazid (Rifinah, sanofi-aventis) and rifampicin + isoniazid + pyrazinamide (Rifater, sanofi-aventis) are preferred. Adverse reactions are seen in about 10 per cent of those treated and may include damage to the nervous system, nausea and vomiting, flu-like reactions, liver problems and skin rash. The main problem with standard therapy is the length of time (six months) for which medication must be taken, which may result in missed doses, and treatment failure, due to the development of resistance to one or more components of the treatment.

***Figure* 1: Robert Koch (1843-1910), the German bacteriologist who identified the bacterium responsible for tuberculosis, for which he received the Nobel prize in 1905.**

In a small percentage (about 1 per cent) of cases in the UK, the TB organism may have become resistant to several of the medicines used for standard therapy. Treatment in this case will be carried out by a specialist, using second-line medicines to which resistance has not developed in the patient concerned. These may include capreomycin, fluoroquinolone antibiotics and others, but these may be either less effective or more toxic than standard therapy. Recently, cases of extremely treatment-resistant TB have been reported outside Western Europe, which is a cause for great concern and makes the development of new medicines an urgent necessity.

For many years, it was standard practice in the UK to vaccinate all schoolchildren with a live attenuated vaccine based on *Mycobacterium bovis* (BCG vaccine) developed by Calmette and Guerin at the Pasteur Institute. However, the efficacy of this vaccination in preventing TB is disputed and has been found to vary greatly from one region to another. BCG vaccination is now recommended only for babies, children and adults considered to be at high risk for TB infection, but not universally. However, there is little doubt that the development of a truly effective new vaccine could be of great public health benefit, especially in developing countries, where infection rates and deaths are high.

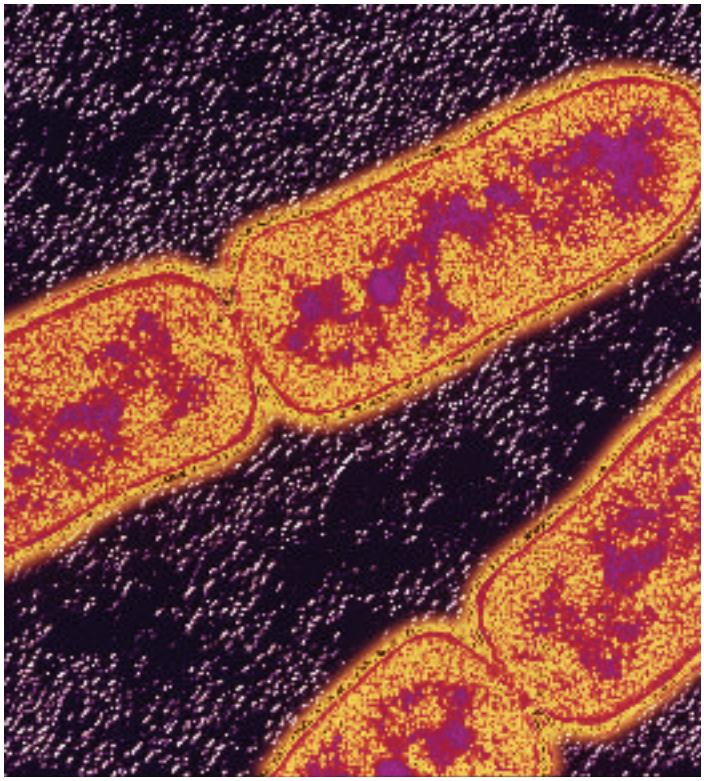

***Figure* 2: Mycobacterium tuberculosis bacteria. The rod-shaped bacteria grow much more slowly than most other bacteria and treatment must be lengthy (6 months) to be sure of killing them.**

What's in the development pipeline?

Development efforts for TB encompass both industry and the private sector and include a number of public-private partnerships. They have benefited from funding from sources such as the Bill & Melinda Gates Foundation, the European Commission and the Wellcome Foundation, among others.

Perhaps furthest advanced in the development of new vaccines for **preventing TB** is an initiative from the University of Oxford Centre for Clinical Vaccinology and Tropical Medicine, supported by the Wellcome Foundation. This vaccine strategy makes use of a 'prime-boost' approach in which an initial vaccination with standard BCG vaccine is followed by a boosting dose of a modified vaccinia virus, Ankara strain (MVA), containing an antigen that is present in all strains of BCG. This BCG/MVA85A vaccine has been found to give strong immune response in Phase 1 trials and is now in Phase 2 testing in South Africa, as well as in Phase 1 trial in the UK in people also infected with HIV.

Also in Phase 2 trial is the Mtb72F/AS02A vaccine under development by GlaxoSmithKline together with the Aeras Global TB Vaccine Foundation. In Phase 1 trials, vaccination with this vaccine has produced strong and persistent cellular and antibody responses.

The third TB vaccine in clinical trial is also the subject of a partnership between Aeras and Crucell. The Ad35 recombinant vaccine is now entering Phase 1 safety testing.

New compounds for **treating TB** are also in development. Bayer and the Global Alliance for TB Drug Development (TB Alliance) have launched a Phase 2 trial to investigate the potential of the existing fluoroquinolone-type antibiotic moxifloxacin (Avelox) to shorten the standard six-month treatment, which would help to improve its effectiveness. Another fluoroquinolone antibiotic, gatifloxacin, (not currently available in the UK) is also under study in a WHO/EU funded Phase 3 trial for TB treatment.

Most other new treatments are in Phase 1 trial. TB Alliance is testing PA-824 and Sequella has the antibiotic SQ109, which enhances the action of isoniazid and rifampicin, and may therefore help shorten the treatment period. SciClone's SCV-07 has reached Phase 2, while other compounds at Phase 1 include the pyrrole LL 3858 (sudoterb, Lupin), OTC 67683 (Otsuka) and Tibotec's TMC 207.

Research into new vaccines and treatments for TB is now much more active than it has been for many years, and it is to be hoped that this will help overcome the enormous global public health burden that this disease, a feared killer throughout the ages, represents.

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V

VACCINES

What are vaccines?

Vaccines are substances injected into the body in order to produce an immune response. Usually, the substance is a bacterium or virus (or some component of one) that has been made harmless, and the objective is to produce a protective immunity in the individual. Later exposure to the full infectious organism then does not result in disease. Examples of infectious diseases commonly prevented by vaccination include tetanus and diphtheria, polio and hepatitis B.

Recently, therapeutic vaccines have come under development, especially for use in cancer. By priming the immune system to respond to an antigen (a substance that stimulates an immune response) that otherwise does not trigger it sufficiently, or at all, such as an antigen on the surface of a tumour, the immune system can be helped to destroy cancer cells. Such an approach might also be used to treat some infectious and other diseases.

Vaccination for disease prevention goes back almost 300 years in the UK, to inoculation to protect against smallpox, and builds upon the insights of pioneers such as Jenner, Pasteur and Robert Koch. The contribution of the pharmaceutical industry has been immense in developing vaccines with high levels of protective efficacy, improved storage stability and few side-effects. They are now manufactured on a scale that makes it possible to protect entire populations against diseases that were feared by earlier generations. Over the past twenty years, biotechnology has made an important contribution to this process, so that highly effective vaccines can be made without handling dangerous pathogens (organisms that cause disease). Such vaccines are often also better tolerated than the older vaccines that contained whole infectious organisms.

NEW SINCE 2000

2001 - Meningitis vaccine (ACWY Vax, GSK)

2001 - Pneumococcal vaccine, 7-valent (Prevenar, Wyeth)

2002 - Varicella vaccine (Varilrix, GSK)

2004 - DTP-Polio (Infanrix-IPV, GSK)

2004 - Cholera vaccine, oral (Dukoral, Novartis)

2006 - Meningitis + Hib vaccine (Menitorix, GSK)

2006 - Rotavirus vaccine (Rotarix, GSK)

***Figure* 1: Louis Pasteur, the pioneering French bacteriologist who introduced the first vaccines against anthrax and rabies.**

Who are vaccines recommended for?

Vaccination is used to prevent epidemics and to protect susceptible individuals against the risk of serious infectious diseases, especially where no treatment is available. It is especially appropriate for three main groups:

- children, to prevent childhood infections with potentially severe complications
- healthy adults travelling to areas of high prevalence of diseases such as hepatitis or typhoid fever
- at risk adults, such as the elderly or those taking immuno suppressive medication, who may suffer serious consequences from a disease that would not normally be severe in others.

In some instances, vaccination may be effective even when given after exposure to the organism that caused it. This is the case for rabies and tetanus, for example. Passive immunisation through injection of a specific antibody may be used to give short-term protection against an expected threat of infection, but such protection only lasts for a few weeks, until the antibody is cleared from the system. Vaccination is required for long-term immunity.

Figure 2: **Modern large-scale vaccine production using advanced cell culture techniques**
(Courtesy of GSK Biologicals)

Present vaccines and their shortcomings

Vaccines are available for a variety of bacterial diseases, including cholera, diphtheria, typhoid fever, tetanus, tuberculosis, whooping cough (pertussis), pneumococcal pneumonia and bacterial meningitis. Vaccine-preventable viral diseases include hepatitis (A and B), measles, mumps, German measles (rubella), polio, rabies, influenza, tick-borne encephalitis, rotavirus, chickenpox and yellow fever.

In the UK, it is recommended that infants should be vaccinated at the age of two to four months against diphtheria, tetanus and pertussis (DTP), Haemophilus influenzae b (Hib), polio and type C meningococcal meningitis. This is normally followed at 12-15 months by vaccination against measles, mumps and rubella (MMR), with booster vaccinations for DTP and polio and MMR at three to five years. Vaccines are normally given by injection and combination products, such as DTP-Polio (Infanrix-IPV, GlaxoSmithKline and Repevax, Sanofi Pasteur MSD), have been developed to enable simultaneous vaccination against several diseases with the minimum number of injections.

Take-up of vaccinations is high, with 94 per cent of children immunised against DTP, Hib and polio, 93 per cent against meningitis C and 84 per cent against MMR by their second birthday, according to NHS statistics for England for 2005/06. The effectiveness of vaccination is shown by figures for the meningitis C programme, in which vaccine was given to those aged 15-17 as well as to infants in their first year, which show a 90 per cent drop in the number of cases of this potentially fatal disease in the targeted groups. Take-up of MMR fell following allegations of a link with autism in 1998, but has since begun to recover.

In adult life, vaccines are usually given to protect people travelling to less developed countries. Vaccines against hepatitis A, typhoid and yellow fever are commonly given for this purpose. However, the vaccine for hepatitis A must be given as two doses at an interval of 6-12 months and many people, realising the need for vaccination only a short while before travelling, do not return for the second injection, limiting the effectiveness of protection. Hepatitis B is another disease in which vaccines are of value, but the UK, unlike many other countries, does not include hepatitis B in the vaccination schedule for infants. Thus, when they reach sexual maturity, many young adults are at risk of this disease, which may have serious long-term consequences, including liver cancer. (See *Hepatitis*)

At the other end of the age-range, influenza vaccination now covers over 75 per cent of those aged 65 or older who are judged to be at high risk of complications if infected, continuing a rising trend over the past decade. However, there are other infections, where vaccination is not currently offered in the UK, such as pneumonia, that have a high death rate in this age group that are also vaccine-preventable (see *Respiratory Infections*).

Figure 3: **A high coverage of childhood vaccination is vital for the prevention of diseases such as whooping cough, measles, polio and meningitis.**

Figure 4: **Annual influenza vaccination in high-risk groups such as those over 65 has now reached 75 per cent coverage.**

Most modern vaccines are well tolerated, with soreness at the injection site and mild, flu-like reactions the most common side-effects. Convulsions may occur following vaccination against whooping cough, but this is rare. The main shortcomings of existing vaccines are that a small number of individuals may fail to develop a protective response to a given vaccine and that vaccines are lacking for a number of significant diseases - most notably HIV and malaria.

What's in the development pipeline?

Major suppliers of vaccines in the UK are Sanofi Pasteur MSD, GlaxoSmithKline, Wyeth and Novartis, and each of these has extensive research programmes for developing new vaccines. Other companies also active in vaccine research include Solvay, Baxter, Crucell, Xenova and Acambis. Because of the large number of projects in this field, only a selection are discussed below. Further discussion of individual vaccines will also be found in other sections of this booklet. (See *Hepatitis, Herpes, HIV and AIDS, Malaria, Respiratory Infections* and *Tuberculosis*.)

In the area of **bacterial infections**, GSK has a vaccine (Synflorix) against *Streptococcus pneumoniae* under development for prevention of respiratory infections in children (Phase 3). The same company also has a combination paediatric vaccine (Globorix) in Phase 3 trial that protects against diphtheria, tetanus, whooping cough, hepatitis B, *Haemophilus influenzae* type b (Hib) and *Neisseria meningitis* types A and C. Also in Phase 3 trial is a separate vaccine that protects against meningitis due to Hib and *Neisseria meningitis* types C and Y.

Following the addition of Prevenar to the routine childhood vaccination schedule, Wyeth is developing a version of this vaccine for children (Phase 3) and for 'high-risk' adults (Phase 2) that protects against a larger number (13) of bacterial strains. Novartis (Phase 2) and Sanofi-Pasteur MSD (Phase 1) are both testing vaccines against a form of meningitis (type B) for which there is no currently available vaccine. In other developments, Acambis has a vaccine in Phase 1 development against *Clostridium difficile*, which is the cause of widespread and difficult-to-treat infections in hospitals, and Merck Sharp & Dohme has a vaccine (MK-V710) that is directed against infection by *Staphylococcus aureus*, a dangerous bacterium, also in Phase 1 trial.

There is much development work ongoing in the field of **viral diseases**. Rotavirus is the most common cause of severe diarrhoea in children and the recent introduction of Rotarix (GSK) is a step forward. Merck Sharp & Dohme also has a rotavirus vaccine (RotaTeq), while Sanofi Pasteur has a vaccine for the prevention of transmission of cytomegalovirus from mother to baby in Phase 2 development.

Gardasil (Sanofi-Pasteur MSD) is a vaccine against four strains of human papillomavirus, the cause of genital warts and cervical cancer. Both this and the vaccine developed by GSK (Cervarix) have been shown to be highly effective in preventing new infections, and should help to reduce the incidence of cervical cancer, which causes more than 1,000 deaths a year.

Other antiviral vaccines in development target a number of tropical diseases. In Phase 3 trials, Acambis has ChimeriVax-JE, a single-dose vaccine against Japanese encephalitis, a disease affecting the brain, which is the leading cause of childhood encephalitis in Asia. Novartis also has a Japanese encephalitis vaccine (IC51) in Phase 3 trial. Acambis is also studying a vaccine against West Nile virus in Phase 2 trial, as is Vical. Hawaii Biotech is just starting Phase 1 trials with its West Nile virus vaccine. At Phase 2, GSK and Sanofi-Pasteur MSD are both working on vaccines against Dengue fever, a painful and disabling infection spread by mosquitoes. Lastly, Crucell and Vical each have vaccines in Phase 1 trial against the deadly Ebola virus, endemic in central Africa.

Therapeutic vaccines are intended to enhance the treatment of various diseases, especially cancer, and are the other focus of new developments. GSK, Oxford BioMedica, Oxxon Therapeutics and sanofi-aventis are all active in this area. GSK has a vaccine against lung cancer and melanoma (MAGE-A3) in Phase 2 trial and a vaccine against prostate cancer (P501) at Phase 1. Oxford BioMedica is developing its 5T4 vaccine TroVax for the treatment of colorectal carcinoma and renal cell carcinoma. Oxxon Therapeutics, meanwhile, has reported responses in nearly 20 per cent of patients with advanced melanoma in Phase 2 trials of its Hi-8 MEL therapeutic vaccine. Sanofi-aventis's candidate vaccine against melanoma is still at the preclinical stage.

Vaccination is likely to remain the best defence against many viral infections and, with the increase in antibiotic resistance, also against many bacterial infections. Only vaccines have the ability to both extinguish ongoing epidemics of infectious diseases and prevent their recurrence. Research into new areas such as cancer therapy represents an exciting and promising new venture with this class of medicines.

Glossary

Acetylcholine: One of several neurotransmitters found in the brain and nervous system
ACE: Angiotensin Converting Enzyme - an enzyme involved in blood pressure regulation
Adjuvant: A substance added to a vaccine that does not itself stimulate the immune system, but which intensifies the immune response to the main vaccine component
Agonist: A medicine that acts on cell receptors and which can mimic the action of a natural hormone, neurotransmitter or other bioactive substance
Analogue: A medicine that shares the same main structure as another medicine, but which differs from it by one or more small modifications
Angiogenesis: The formation of new blood vessels, often after damage or injury
Antagonist: A medicine that acts on cell receptors and blocks the action of a natural hormone, neurotransmitter or other bioactive substance
Antibody: A large protein belonging to one of five major classes produced by lymphocytes of the immune system which binds selectively to an antigen, for example an infectious agent, to neutralise it
Artery: Blood vessel carrying oxygenated blood from the heart to the organs of the body
Cardiovascular: Describes the heart, blood vessels and circulatory system
Cerebrovascular: Term denoting the blood vessels carrying blood to the brain
Cholesterol: The most abundant steroid in animal tissues. Found in blood plasma, where it is a major contributor to the development of plaque
Chronic: Long-lasting or persistent (disease)
Cognition/cognitive: Mental processes such as perception, remembering, judging and reasoning; having to do with thinking
Cytokine: General term for proteins that transmit stimulatory or inhibitory messages between cells. They include interferon, interleukin, and colony stimulating factors
Cytotoxic: A medicine that kills cells - especially used in cancer therapy
DNA: Deoxyribonucleic acid - the long string of nucleotide `letters' that make up the `building blocks' of genes
Dopamine: One of several neurotransmitters found in the brain and nervous system
Diuretic: A medicine that increases the amount of urine excreted
Enzyme: A protein in cells and tissues that catalyses a metabolic or other chemical reaction
Exacerbation: A worsening, or flare-up, of an existing condition
Formulation: The form of a medicine - e.g. injection, tablet, spray, lotion, etc
GABA: Gamma-amino butyric acid, one of several neurotransmitters found in the brain and nervous system
Gastrointestinal: Referring to the stomach and/or intestines; the digestive tract
Genome: The complete complement of genes unique to a given species
Heparin: An anticoagulant naturally produced in the body, especially the lung and liver
Hormone: A chemical messenger produced and secreted by cells or tissues. It may act locally or through circulation in the blood
Hypertension: High blood pressure
Indication: A situation for which a medicine is recommended to he used
Inhibitor: A substance that attaches to a receptor site to inhibit the action of an enzyme
Insulin: A hormone produced by the beta cells of the pancreas that is essential for the utilisation of glucose. Widely used to treat diabetes
Interferon: One of a family of cytokines that have antiviral and immune modulating actions
Interleukin: One of a family of about 12 cytokines involved in signalling between cells of the immune system
In vitro: Tests carried out at the cellular level in the laboratory
Lesion: Damage or injury to body tissue or organ
Metabolic/metabolise: The processes by which substances are changed in the body
Metastasis/metastatic: The process by which cancerous cells spread from a tumour into surrounding tissue and (via the blood) to other body organs
Monoclonal antibody: A highly specific antibody (see above) derived from a single group of identical cells which recognises only one kind of antigen
MRI: Magnetic Resonance Imaging, a diagnostic system for the scanning body tissues
Neuropathic pain: Pain that arises from damage to the nerves or brain rather than body tissues
Neurotransmitter: One of several substances in the brain and nervous system that carry impulses from nerve to nerve
Noradrenaline: One of several neurotransmitters found in the brain and nervous system
Pathogen: A disease-causing agent; most usually a bacterium, virus or fungus
Placebo: An inactive substance used in a clinical trial as a comparison with a test medicine
Platelet: Small structures found in the blood which clump together during blood clotting
Prostaglandin: A type of lipid (fat) with one or more biological actions such as causing muscle contraction or pain, or affecting blood pressure. Prostaglandins are often involved in inflammation
Protease: An enzyme found in many tissues and micro-organisms that can cut up proteins into smaller components
Receptor: An important structural protein on cell surfaces that binds specific factors such as hormones, antigens, or neurotransmitters, triggering some cellular event
Recombinant: Describes compounds created through genetic engineering
Remission: A period in which signs of a chronic disease disappear, although the disease itself may not be cured
Serotonin: One of several neurotransmitters found in the brain and nervous system
Statins: A group of compounds able to reduce the circulating levels of cholesterol
Systemic infection: One affecting the body as a whole - not a localised infection
Therapeutic vaccine: A vaccine that is designed to treat a condition, rather than prevent it
Topical: A form of a medicine (e.g. a cream) intended for spreading on the skin
Triglyceride: A type of neutral lipid found in vegetable oil and animal fats that contains three (often different) fatty acids bound to glycerol. Triglycerides are found in blood and are stored in fat cells as a source of energy
Vector: A carrier, often a virus or other organism, by which a genetically engineered medicine is conveyed to its target, where it unloads its genetic information
Vein: A blood vessel that returns de-oxygenated blood to the heart from an organ

	Alzheimer's disease	Anxiety	Asthma	Atherosclerosis	Bacterial infections	BPH	Bipolar disorder	Cancer	Cardiac Arrhythmia	Congestive heart failure	C&I	COPD	Cystic fibrosis	Depression	Diabetes	Epilepsy	Fungal infections	Hepatitis (viral)	Herpes
Abbott	●			●	●			●		●					●				
Acambis																			
Alizyme								●							●				
Amgen		●						●		●					●				
Astellas			●		●	●		●	●	●					●		●		
AstraZeneca	●	●	●	●	●		●	●	●	●		●		●	●				
Bayer				●	●			●				●			●				
Boehringer Ingelheim								●				●		●					
Biogen-IDEC								●											
Bristol-Myers Squibb	●						●	●	●					●	●			●	
Cephalon								●											
Chugai															●				
Daiichi-Sankyo			●		●			●				●			●		●		
DaiNippon-Sumitomo	●		●	●										●	●				
Dov Pharma														●					
Eisai	●				●			●							●	●			
GenMab								●											
Genzyme					●			●											
Gilead																		●	
GlaxoSmithKline	●	●	●	●	●	●	●	●	●	●		●		●	●	●		●	●
GW Pharma															●				
Human Genome Sciences								●							●				
Ipsen	●							●							●				
ISIS				●				●							●				
IVAX						●										●			
J&J	●	●			●		●	●						●		●			
Kowa				●											●				
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Lilly	●	●		●		●	●	●			●			●	●			●	
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Merck Pharmaceuticals								●							●				
Millennium Pharma				●				●											
Mitsubishi Pharma		●								●					●			●	
MSD	●	●		●	●			●						●	●		●		
Novartis	●	●	●	●	●		●	●		●		●	●	●	●		●	●	
Novo Nordisk								●							●				
Ono Pharma	●	●	●									●		●	●				
Organon		●					●				●			●					
Otsuka							●			●		●							
Oxford BioMedica								●											
Oxxon Therapeutics																		●	
Pierre Fabre		●				●		●						●					
Pfizer	●	●	●	●	●	●	●	●				●		●	●		●	●	
PharmaMar								●											
Roche	●	●	●	●	●			●			●	●		●	●		●	●	
Sanofi-aventis	●	●	●	●	●	●	●	●	●	●		●		●	●	●	●		●
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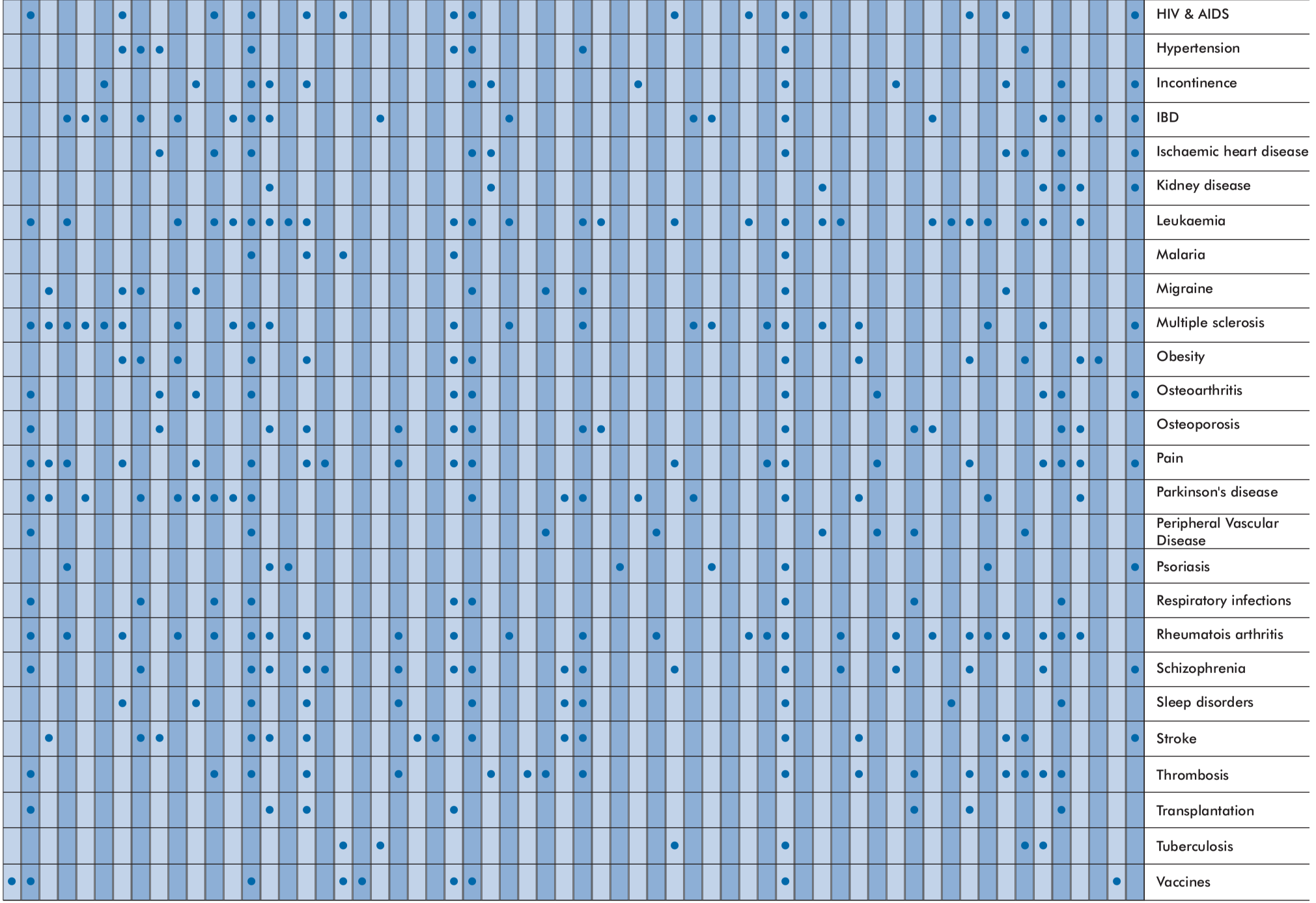
Schering-Plough					●			●				●					●	●	
Schwarz Pharma																●			
Serono								●			●				●			●	
Servier		●		●			●							●	●				
Solvay							●		●	●									
Takeda				●	●			●							●				
Tanabe			●					●	●		●	●			●				
TEVA	●													●					
UCB	●		●					●						●		●			
Vernalis																			
Wyeth	●	●	●		●		●	●	●		●			●	●			●	
Xenova								●											


HIV & AIDS
Hypertension
Incontinence
IBD
Ischaemic heart disease
Kidney disease
Leukaemia
Malaria
Migraine
Multiple sclerosis
Obesity
Osteoarthritis
Osteoporosis
Pain
Parkinson's disease
Peripheral Vascular Disease
Psoriasis
Respiratory infections
Rheumatois arthritis
Schizophrenia
Sleep disorders
Stroke
Thrombosis
Transplantation
Tuberculosis
Vaccines

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