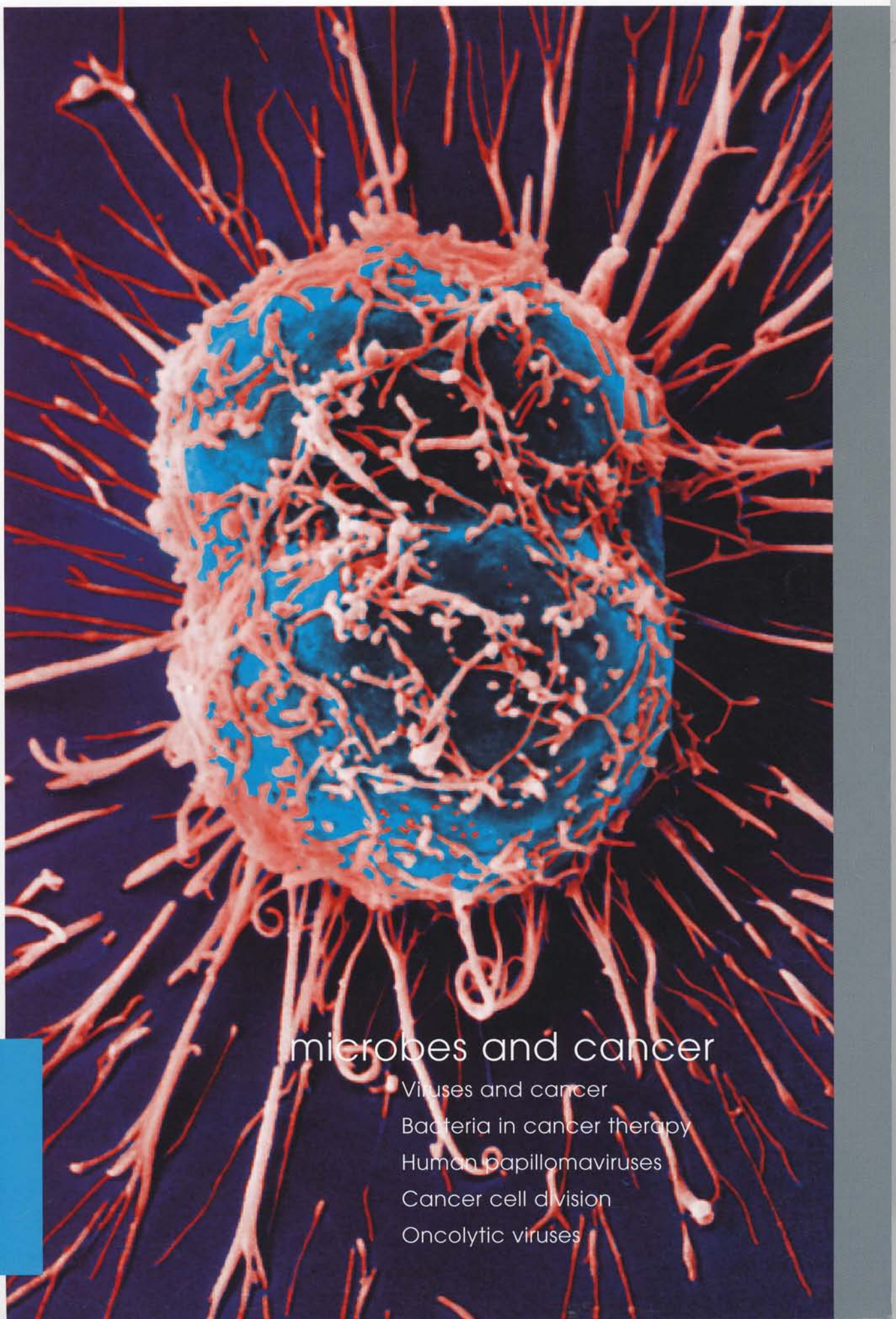
microbiologytoday

vol32 | aug05
quarterly
magazine of
the society
for general
microbiology



microbes and cancer

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Cover image Coloured scanning electron micrograph of a dividing cervical cancer cell. *Steve Gschmeissner / Science Photo Library*

Editor Dr Gavin Thomas Editorial Board Dr Sue Assinder, Dr Pauline Handley, Professor Iain Hagan Managing Editor Janet Hurst Assistant Editor Faye Jones Design & Production Ian Atherton Contributions are always welcome and should be addressed to the Editor c/o SGM Headquarters, Marlborough House, Basingstoke Road, Spencers Wood, Reading RG7 1AG Tel. 0118 988 1809 Fax 0118 988 5656 email mtoday@sgm.ac.uk web www.sgm.ac.uk Advertising David Lancaster, McMillan-Scott PLC, London Office, 10 Savoy Street, London WC2E 7HR Tel. 0207 878 2316 Fax 0207 379 7118 email david@mcmslondon.co.uk Regular feature images pp. 103 *SGM*; 137 *Imperial College London/SPL*; 139 *Mauro Fermariello/SPL*; 143 *Stockbyte/Photolibrary.com*; 145 *Taxi/Getty Images*; 147 *Simon Lewis/SPL*; 151 *Tek Image/SPL*; 155 *Digital Vision/Getty Images*

 ISSN 1464-0570 Printed by Latimer Trend & Company Ltd, Plymouth, UK

news

SGM takes a lead in European microbiology education

At the end of June the Society was delighted to act as host to 11 microbiologists from different European countries who were all eager to learn how to promote microbiology in their local schools. The visitors, who were generously sponsored by the Federation of European Microbiological Societies (FEMS), attended a course held at Reading University. They joined UK teachers and technicians on one of the SGM's Basic Practical Microbiology courses tutored by the usual dynamic combination of the two Johns (Grainger and Schollar), followed by a second day of talks and discussions on ways of promoting microbiology education. Education Officer Sue Assinder and Convener of the Education & Training Group, Jo Verran, took part, alongside SGM staff Janet Hurst and Dariel Burdass who organized the event. With falling recruitment to microbiology degree courses across Europe and the need to educate the public about the subject in the light of many issues that affect their lives, increasing the amount of microbiology taught in schools has never been more important. It is hoped that this will be the first of a series of joint initiatives between the Society and FEMS in this arena.

SGM wins silver at the RHS Chelsea Flower Show.

The SGM's display on beneficial interactions between microbes and plant roots at the RHS Chelsea Flower Show attracted the attention of thousands of visiting gardeners. It also pleased the judges, as you can read on p. 146.


THE ROYAL HORTICULTURAL SOCIETY

Established 1804 Incorporated 1809

SILVER MEDAL

CHELSEA FLOWER SHOW 2005

Awarded to Society for General Microbiology

For an exhibit of Plants & microbes living in harmony

IN THE LINDLEY RANGE

New Treasurer

Professor Colin Harwood

As destiny would have it, I grew up in Fleming Court, Paddington, just round the corner from St Mary's Hospital and named after SGM's first President. I first became interested in microbiology as an undergraduate at London University and my PhD with Simon Baumberg at Leeds started my love affair with *Bacillus* spp. I was a post-doctoral fellow with the Meynells at Kent and had a sabbatical with a biotech company in Sweden. I am currently Professor of Molecular Microbiology at Newcastle University.

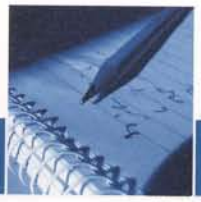
My research is on gene regulation and protein secretion in *B. subtilis* and *B. anthracis*. I have extensive collaborations with colleagues in Europe and Japan (my favourite destination), currently coordinating an EU FP6 project on bacterial responses to host-mediated stresses.

I have been a member of SGM since 1973, previously serving twice on Council. I have also served on the committees of the Genetics Society, the Society for Applied Microbiology and the European Federation of Biotechnology. I have a strong belief in the role and value of learned societies and look forward to working with colleagues at Marlborough House, in academia, the public services and industry to develop still further the Society's activities in promoting '*the science and significance of microbiology*'.

Annual General Meeting 2005

The Annual General Meeting of the Society will be held on **Tuesday 13 September** at the Society meeting at Keele University.

Agenda papers including reports from Officers and Group Conveners and the accounts of the Society for 2004 are in the separate booklet distributed to all members with this issue of *Microbiology Today*.



News of members

Congratulations to **Bob Rastall**, convener of the Food and Beverages Group, on the award of a personal chair as Professor of Biotechnology at the University of Reading.

Deaths

The Society notes with regret the deaths of **Professor E.F. Gale** (original member and President 1967–1969; see obituary on p. 152), **Professor B.A.D. Stocker** (member since 1949 and served on Council 1957–1961 and 1965–1966), **Dr H.R. Smith** (member since 1973) and **Dr D. Tyrrell** (member since 1955).

May Council meeting

SGM strategy

The President reported on the outcome of the Strategy Group meeting attended by elected members and officers of Council in Aberdeen in March. Various issues were discussed, including the preparation of SWOT analyses of the SGM and of microbiology in the UK; SGM publications development; interactions with other microbiological organizations, including joint meetings; Society finances and public awareness of microbiological issues and their promotion by the SGM. Council concurred with the Group's recommendations. It also agreed to set aside periods devoted to the discussion of strategic issues at future Council meetings.

Council and Group elections

It was noted that, due to the healthy number of nominations, elections will be necessary to fill the three up-coming vacancies for elected members of Council and various places on Group committees. Members should have received their ballot papers and are urged to use their votes.

Microbiology

The President thanked **Professor Chris Thomas**, Birmingham, the outgoing Editor-in-Chief of *Microbiology*, for all his hard and diligent work in collaboration with the Editors and editorial staff, and for maintaining and developing the healthy state of the journal. **Professor Charles J. Dorman**, Dublin, was welcomed to Council as his replacement.

Bye-law change

Council approved a change to the Bye-laws enabling Group committees, if they wish, to co-opt a member from industry in addition to the normal number of committee members, to serve for periods of 1–2 years. This action has been taken as part of the Society's policy to strengthen its links with industrial microbiologists.

SGM Finances

The year-end forecast is currently that the SGM budget will break even or have a very small surplus, in accordance with Council policy and the Society's status as a charity. Council members were also gratified to see from graphs how the Society's income from journal subscriptions and investments had enabled a significant increase in SGM activities (meetings, journals, grants, public awareness and education) to be funded over the past 10 years.

Microbiology awareness and education

Council was pleased to learn of the success of the event held at the House of Lords in March to raise awareness of current important infectious disease issues. They also heard from the Education Officer that new careers literature and teaching resources were now available, adding to the already impressive range of material that the SGM distributes to promote microbiology in schools.

Ulrich Desselberger
General Secretary

Industrial Member Forum

Some industry-based members took the opportunity to meet with Group representatives and Council members at the Society's conference at Heriot-Watt University in early April. They discussed strategies to increase representation of industrial microbiologists on Group committees and looked at ways of making the content of symposia more relevant to industry-based scientists. The forum concluded with a reception. A full report is available from Jane Westwell at Marlborough House (j.westwell@sgm.ac.uk).

As a result of the discussions, External Relations Office staff are planning a practical workshop to tie in with a symposium at a forthcoming meeting and the Food & Beverage Group Committee has welcomed John Rigarlsford as its first co-opted member.

The Industrial Member Forum has been a useful exercise and has given us food for thought. We extend thanks to those members who have given up their time to join in the discussions.

Staff news

Judith Rowlands

In May we were very sorry to say goodbye to Judith Rowlands, who has taken retirement from her post as Accounts Assistant. Judith started work at SGM in December 1994 and has seen many changes in both the Society and accounting procedures since that time of dot-matrix printers and hand-written ledgers. Our finances have been in very safe hands, thanks to Judith's legendary meticulousness, amazing processing powers and accuracy. Over the years she must have handled thousands of expense claims forms for speakers, Group committees and Council members in a very timely manner. In addition to processing invoices and claims, Judith also managed the staff payroll and bank reconciliations, providing the basic data for the audited accounts. She has worked closely with Finance Manager, Richard Noble, to implement new automated systems that have streamlined all aspects of the job.

Although office-based, Judith enjoyed her outings to SGM meetings where she will be remembered by delegates as the friendly person behind the conference desk who took their money! Always pleasant, professional and courteous, many members will be grateful to Judith for her help with financial queries.

The Treasurer acknowledged Judith's contribution to the success of the Society at the last Council meeting. On her last working day we all gathered at the pub for lunch to wish Judith well and present her with cards from the staff and Council members, together with gifts of a table lamp and book tokens.

In addition to her work for SGM, Judith also ran the FEMS accounts and she will continue to do this job from home. We wish her a long and happy retirement.

New staff

We are pleased to welcome **Geraldine Pearce** as the new Financial Accounts Assistant. She comes to the SGM after a range of similar posts in commercial companies.

40th birthday celebrations

Microbiology Today Production Editor Ian Atherton's recent big birthday was cause for celebrations in the office. Despite the looming print deadline, he was able to take a little time out to receive gifts and cards from the staff and to partake of a lunch at the local Indian restaurant. Ian is responsible for the design and setting of virtually all of our publicity material, meetings literature, the annual report and many of the educational resources as well as *Microbiology Today* and the symposium volume series. This is in addition to his role as Staff Editor of *Microbiology*. Ian has worked at the SGM since 1990.

Food Standards Agency

www.food.gov.uk

New Science Strategy

The FSA wants views on a new draft science strategy that seeks to identify the scientific evidence it needs during the next 5 years to inform its policies. The deadline for responses is **29 August 2005**.

£100m for local authorities to promote food safety

The FSA is offering grants to local authorities in England to help catering businesses to implement its new '*safer food, better business*' initiative. New legislation requires all food businesses to put in place food safety management systems based on HACCP principles.

DEFRA consultations

UK government department DEFRA has several consultations underway.

Amendments to the Specified Animal Pathogens Order 1998

(http://www.defra.gov.uk/corporate/consult/animal-pathogens/index.htm). Deadline **30 August 2005**

Foot-and-Mouth Disease Directive

(http://www.defra.gov.uk/corporate/consult/fmd-directive/index.htm). Deadline **1st September 2005**

Proposed EC Directive on controls for avian influenza

(http://www.defra.gov.uk/corporate/consult/avian-flu/index.htm). Deadline **11th August 2005**

Comments are welcome from SGM members on any of these proposals. Please contact Professional Affairs Administrator Faye Jones if you are not already registered on the Experts Database.

Prize Lectureships

Fred Griffith Review Lecture

Professor David Ellar

Title of Lecture: *Bioengineering beneficial* Bacillus *toxins*

After gaining his PhD from Syracuse University, New York, studying *Bacillus* sporulation, Professor Ellar went to New York University to work on bacterial membranes with Professor Milton Salton. Upon appointment to the Biochemistry Department at Cambridge he began to compare the biochemistry of developing, dormant and germinating *Bacillus* spore membranes and showed that activation of a cortex-lytic enzyme by the germinant is a triggering mechanism for spore germination. In 1980 he began investigating two groups of insecticidal proteins (Cry and cyt delta-endotoxins) synthesized by *Bacillus thuringiensis* during sporulation. These 'biopesticides', which destroy gut epithelial cells, are alternatives to chemical pesticides either as sprays or in transgenic plants. At the outset, relatively little was known of the structure, genetics or mode of action of these toxins. In the dramatic improvement in this picture in the succeeding 25 years, his laboratory has played a major part as a leading international centre for research on these toxins. By combining the 'killing' domains of the Cry toxins with a diverse library of human antibody recognition domains, the group is constructing novel immunotoxins – 'Crybodies' – that can target selected cells for destruction.

Peter Wildy Prize for Microbiology Education

Professor Joanna Verran

Title of Lecture: *Yes, but is it microbiology?*

I left the far south west of Cornwall for university 'up North'. My first degree was in Bacteriology and Virology at the University of Manchester, followed by an MSc and PhD in the same department. My PhD investigated the effect of a novel sucrose substitute on carbohydrate metabolism and adhesion of *Streptococcus mutans*. While I was doing my PhD, I was asked to do some part time teaching at the Polytechnic – and I really enjoyed it! Subsequently, I was thrilled to get a lectureship at the Poly, directly from my PhD. Now to my horror, a 25 year service medal is almost nigh, and I am Professor of Microbiology in the Department of Biological Sciences at Manchester Metropolitan University.

I was able to maintain research at the Poly, but focused more on microbial attachment to inert materials, since we had dental and polymer technology departments on site. Interdisciplinary research provided a novel niche, and I have been working ever since with chemists, polymer technologists and materials scientists, focusing on the properties of inert substrata which affect attachment, retention and colonization by micro-organisms. In fact, in the last RAE, I was submitted within the Materials Unit of Assessment (we did quite well)! We have been able to apply findings to food, water and environmental microbiology.

I have also taught all aspects of microbiology on a range of courses from HND to PhD. I still enjoy this, and also had fun exploring different ways of encouraging learning of the subject. My latest fascination is with the interactions occurring between microbiology and art, and the potential of this link for conveying scientific principles to a wider audience. Never a dull moment...

UNESCO–IUMS–SGM Fellowships

www.iums.org

Seven Research Fellowships have been awarded, along with three Travel Fellowships under this joint scheme which aims to support young microbiologists in developing countries. SGM continues to provide help for this valuable scheme under its International Development Fund.

Research Council delivery plans

www.rcuk.ac.uk/deliveryplan.asp

The UK Research Councils have simultaneously published their plans and priorities for the next 5 years. During this period they will be administering more than £3 billion a year on research. The BBSRC and MRC plans will have particular relevance to microbiology.

Money for biotech

www.dti.gov.uk

The UK Department of Trade and Industry is to allocate over £1 billion to biotechnology, including help to universities and institutes with spin-off companies to develop their findings. This is part of the Government's £10 billion spending on UK science over the next 3 years.

Grants

Overseas schemes

The deadline is **14 October 2005** for receipt of applications to the following schemes:

- International Research Grants
- International Development Fund
- Watanabe Book Fund

Student schemes

Postgraduate Student Meeting Grants

Applications for a grant to attend the SGM's Keele meeting (12–14 September) must be received by **9 September 2005**, and by **23 September 2005** for a grant to attend the joint SGM/Norwegian Societies meeting (27–30 September).

President's Fund Research Visits

Nine applications were successful in the last round; the second round of applications closes on **14 October 2005**.

SGM has a wide range of grant schemes to support microbiology. See **www.sgm.ac.uk/grants** for details and closing dates.
Any enquiries should be made to the Grants Office, SGM, Marlborough House, Basingstoke Road, Spencers Wood, Reading RG7 1AG (**t** 0118 988 1821; **f** 0118 988 5656; **e** grants@sgm.ac.uk).

Elective Grants

Funding is available for medical/dental/ veterinary students to work on microbiological projects in their elective periods. The closing date for applications is **28 October 2005**.

Other schemes

Seminar Speakers Fund

The Fund supports talks on microbiological topics in departmental seminar programmes. Applications will be dealt with on first come, first served basis during the academic year.

Education Development Fund/ PUS Awards

Grants are available to members for projects intended to lead to an improvement in the teaching of any aspect of microbiology relevant to education in the UK. Funding is also available for small projects to promote the public understanding of microbiology, such as workshops, talks, demonstrations, leaflets, and activities at science festivals. Applications will be considered on a first come, first served basis during the calendar year.

Retired Member Conference Grants

Retired members are reminded that they may now apply for a grant to attend one SGM conference each year. The award covers en-suite accommodation and the Society dinner, up to a maximum of £250. Applications for grants to attend the SGM meeting at Keele University are invited.

Student employability: whose job is it?

Biosciences Federation Education Colloquium
12 October
Victory Services Club, London

What and who makes a bioscience graduate employable? This workshop invites school and university teachers, employers, educational and careers professionals to discuss how schools, universities and industry can enhance student employability. To register see **www.bsf.ac.uk/edu**

The BA Festival of Science

3–10 September 2005
Dublin

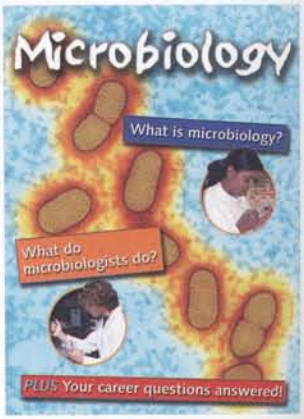
www.the-ba.net/festivalofscience

A packed programme of talks, workshops, debates, sci-art exhibitions, dramatic performances on wide-ranging scientific topics is taking place.

New careers literature

A colourful leaflet and matching poster have been created by Jane Westwell to attract 14- to 18-year olds to a career in microbiology. Designed by Ian Atherton in the style of modern teen magazines, the leaflet provides the answers to 'What is microbiology' and 'What do microbiologists do' before tackling some 'agony aunt' type questions that might be posed by an interested student. Both publications are liberally illustrated with exciting pictures of different types of microbes, and the leaflet also includes photographs of young microbiologists at work.

These materials, along with the 16-page booklet *Your Career in Microbiology*, which covers the subject in depth as well as containing profiles of young microbiologists with widely ranging career paths, are ideal for promoting microbiology undergraduate courses in schools. Copies are free from the External Relations Office. Email **careers@sgm.ac.uk** to place an order.



New Group Conveners

Microbial Infection

Dr Nick Dorrell

I originally trained as a pharmacist at the University of Bath and completed my pre-registration training at King's College Hospital in 1989. After 2 years working in hospital pharmacy, I returned to Bath to study DNA repair in *Escherichia coli*, completing my PhD in 1993. I joined Brendan Wren's research group at St Bartholomew's Hospital in 1994, and worked on many different aspects of bacterial pathogenicity in *Brucella* species, *Yersinia* species and *Helicobacter pylori*. I joined the LSHTM in 1999 and continue to study bacterial pathogenicity in both *H. pylori* and *Campylobacter jejuni*.

One of my major interests is developing the new technology associated with functional genomic research, particularly DNA microarrays. I was involved in the construction of the first DNA microarray produced by the Bacterial Microarray Group at St George's and am currently User Group Co-ordinator for both their *C. jejuni* and *H. pylori* microarrays. Current research interests include the functional analysis of the *N*-linked glycosylation system in *C. jejuni* and the innate immune response to *C. jejuni* infection.

Fermentation & Bioprocessing

Dr Chris J Hewitt

I am a Senior Lecturer in the Department of Chemical Engineering at the University of Birmingham, UK. After graduating with a first class honours degree in microbiology from Royal Holloway College, University of London in 1990, I came to Birmingham to read for a PhD working on the synthesis of α-amylase by *Bacillus amyloliquefaciens* in complex and synthetic culture media under the supervision of Professor Gerald Solomons.

Known by my colleagues as a 'sort of a biochemical engineer' I am currently busy further developing the 'Cell factories' research group that seeks to fully understand the interaction of the cell with the process environment for informed process optimization and scale-up. This subject comfortably spans the engineering life science interface, including topics such as recombinant microbial fermentation, animal/insect cell culture, brewing, bioremediation, biotransformation and predictive food microbiology. At the centre of this research is the development of powerful analytical techniques such as multi-parameter flow cytometry, and image analysis that allow the study of organisms at the individual cell level.

ImageBank

www.bioscience.heacademy.ac.uk/imagebank

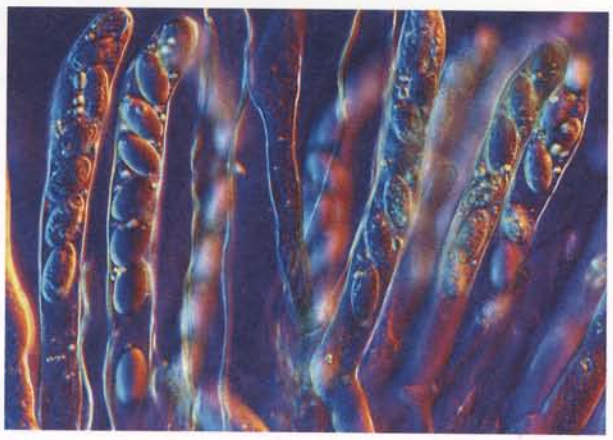
Picture this...

You need a specific image to accompany your lecture or practical session and you don't have time to trawl through pages and pages of copyright-protected images that your internet search engine has dragged up. So where can you go? Have you ever thought about ImageBank?

ImageBank is an online resource provided by the Centre for Bioscience (formerly LTSN Bioscience) giving access to thousands of free, copyright cleared, bioscience images for use by both academics and students for teaching purposes.

The wide variety of images ranges from natural history and histological sections through to lab equipment and techniques; amongst the collections are microbiology images from the University of Leeds. There are links to other biological image sites.

New images for the resource are always welcome. For a limited time, we are offering free digitization of slides and photos contributed to ImageBank.



Contact **imagebank@ltsnbio.leeds.ac.uk**

▲ *Morchella esculenta* asci. *Gordon Beakes © University of Newcastle-upon-Tyne*

A new era for marine microbiology: the opening of the European Centre for Marine Biotechnology

The marine microbiology sector is increasingly becoming the target for new business and research initiatives and the opening of the European Centre for Marine Biotechnology (ECMB; www.ecmb.org) heralds a new era in marine biotechnology for the UK and Europe. Established as a business incubator, and co-located with the Scottish Association for Marine Science (SAMS) in a new £12 million laboratory development at Dunstaffnage near Oban, the centre is the first of its kind in Europe. The Centre represents the coming together of business and research ventures to form a cluster of like-minded scientists and entrepreneurs focused on harnessing marine resources to generate technological advances and solutions.

The Centre was opened on the 5 April 2005 by Baroness Susan Greenfield who expressed hope that this encouraging venture should be viewed as a model interface between academia and industry. The co-location of SAMS and the ECMB enables close collaboration between established researchers and the vibrant new business ventures. Situated in the scenic west coast of Scotland, the ECMB provides excellent access to the marine coastal environment and the open waters of the North Atlantic.

The ECMB hosts a number of companies that exploit the diversity of biological organisms present in the marine environment. One utilizes its specialist skills to discover, isolate and culture new marine bacteria and fungi for discovery of novel compounds as candidates for anti-infectives and as sources of valuable products for the nutraceutical markets. Another, the first marine company to specialize in marine invertebrate glycobiology, identifies products with biochemical and pharmaceuticals applications. Finally, the Culture Collection for Algae and Protozoa (CCAP) (www.ccap.ac.uk) is the longest established of the world's major protistan service culture collections and unique in holding over 2,000 strains of algae and protozoa which are supplied worldwide to industry and the academic community.

***Kate Rowley**, Knowledge Transfer Officer, ECMB*

Elected Fellows of the Royal Society

Congratulations to the following microbiologists who were elected Fellows of the Royal Society recently. Fellows are elected for their contribution to science, both in fundamental research resulting in greater understanding and also in leading and directing scientific and technological progress in industry and research establishments. This year 44 new Fellows were elected.

Stephen John Williams Busby

Professor of Biochemistry, School of Biosciences, University of Birmingham

He is distinguished for his work on the molecular mechanisms that regulate bacterial gene expression, particularly with respect to transcription initiation and to the effects of nutrient availability. Professor Busby is a member of the SGM.

John Collinge

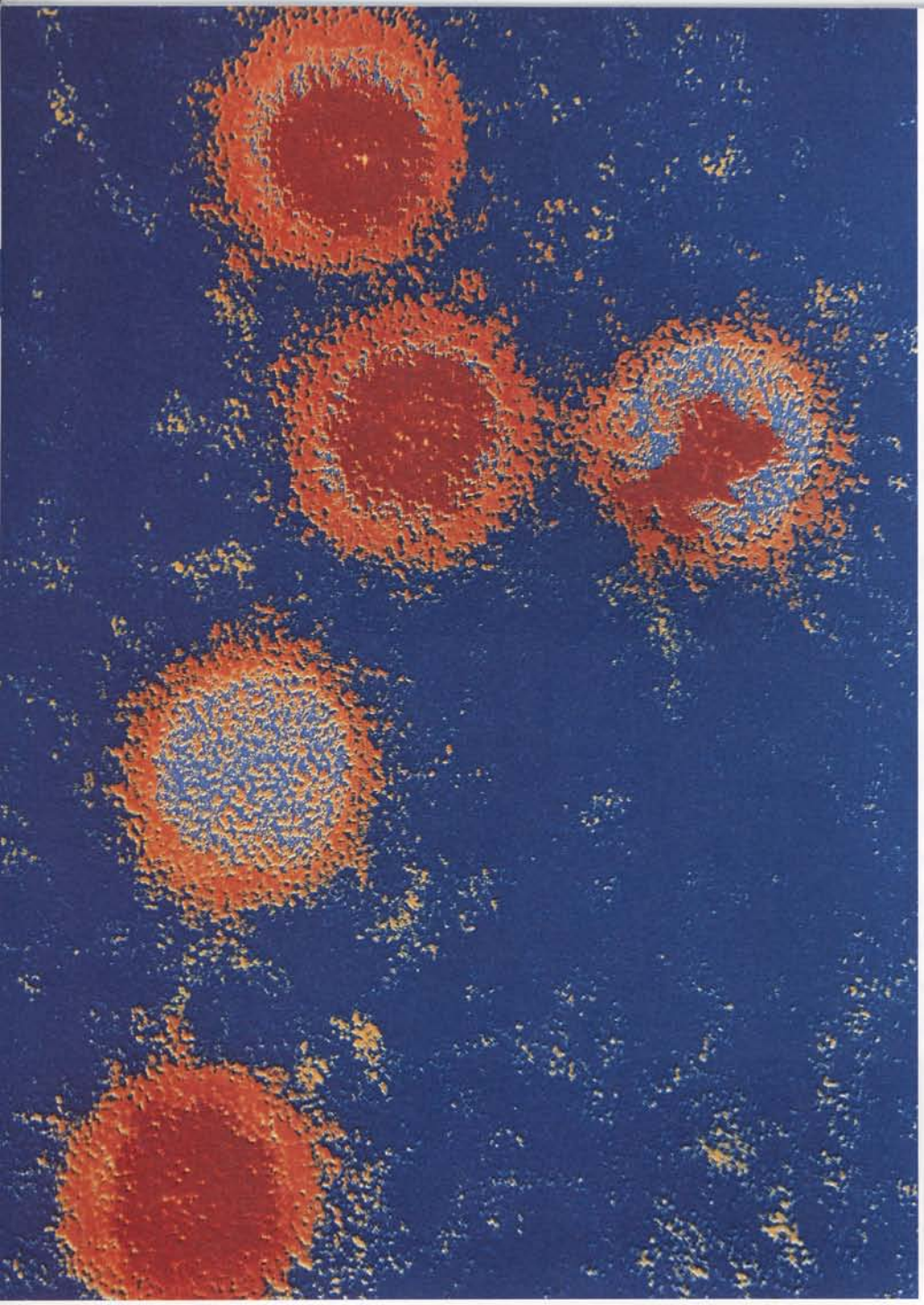
Professor of Neurology and Head of Department of Neurodegenerative Disease, Institute of Neurology, University College London and Director of the MRC Prion Unit

He is distinguished for his work on the molecular basis of prion propagation and strain diversity, and has applied these advances to clinical medicine.

Alastair Hugh Fitter

Professor of Ecology, Department of Biology, University of York

He is distinguished for his contribution to understanding the structure and function of root systems and is particularly recognized for his seminal work on symbioses between roots and fungi which he has shown to be essential for the survival of most plants in nature. Professor Fitter kindly contributed an article on mycorrhizas to the last issue of *Microbiology Today*.



An introduction to viruses and cancer

Viruses are associated with up to 20 % of cancers. **Dorothy H. Crawford** describes how the links were made between viruses and cancer and how current research is leading to the development of vaccines.

Cancer affects around one in three people in Western societies, where, along with heart disease and stroke, it is one of the major killers. Cancer results from the uncontrolled growth of a single cell that eventually forms a clone of tumour cells which may then metastasize (be disseminated) to other sites in the body. Over the years researchers have identified many factors which increase the risk of developing certain types of cancer, such as smoking for lung cancer and sunlight for skin cancer. But since not everyone exposed to these risks develops the cancer, additional factors must be required for the outgrowth of a tumour.

We now know that for a healthy cell to transform into a cancer cell a series of changes must occur which slowly release the cell from the multiple checks and balances which control its normal growth. This chain of events, which involves both genetic changes and environmental factors, explains why cancer may take many years to develop after exposure to a single risk factor and is therefore generally a disease of middle and old age.

The link between viruses and cancer was one of the pivotal discoveries in cancer research

Because cancer development requires several 'assaults' on an individual cell, at the cellular level it is very rare. Each of us has around 10^{14} cells in our bodies with the potential to become a cancerous clone, but only one cell in one third of the population will turn cancerous. So the chance of an individual cell becoming a cancer cell is a vanishingly small 1 in 3×10^{14}.

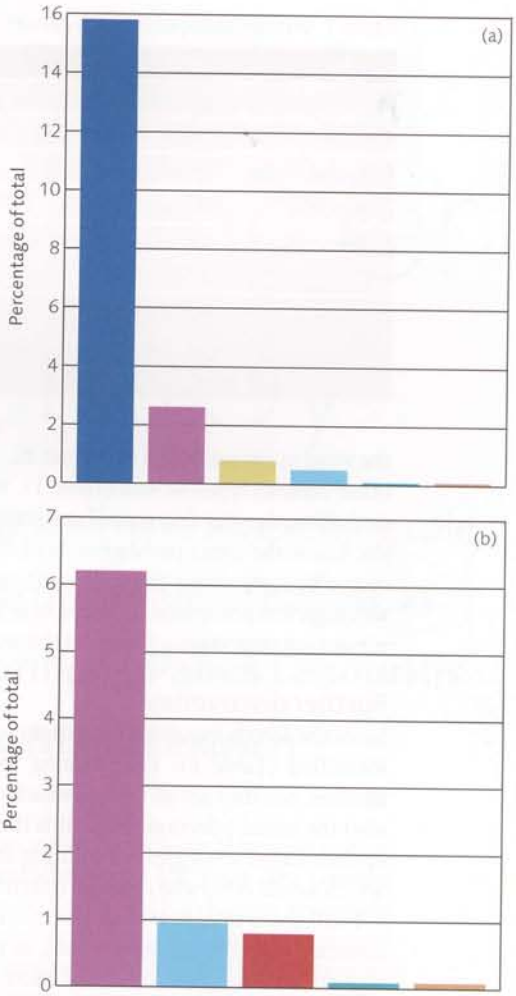
Linking viruses with cancer

The link between viruses and cancer was one of the pivotal discoveries in cancer research. These days it is generally agreed that viruses are involved in 10–20 % of all cancers (Fig. 1). But acceptance of this association took a long time, probably because viruses were perceived as infectious and transmissible whereas cancers were not. As long ago as 1908 two Danish scientists, Wilhelm Ellermann and Oluf Bang showed that leukaemia in chickens was caused by a filterable agent (a virus) which could transmit the disease. And just 3 years later, Peyton Rous, working at the Rockefeller Institute in New York, discovered a virus which caused sarcoma in chickens. Their findings were virtually ignored at the time, although 50 years later (in 1966) Rous received a Nobel prize. By that time several other animal tumour viruses had been discovered and the importance of his early work was finally recognized.

Viruses and human cancers

Following the success of the animal tumour virus field, scientists turned their attention to human tumours, but progress was painfully slow. It was not until the early 1960s that Anthony Epstein, while working on *Rous sarcoma virus* at the Middlesex Hospital, London, attended a seminar in which Denis Burkitt, a British surgeon working in Uganda, described a tumour of the jaw in African children. Although previously unrecognized, this was, and still is, the commonest childhood tumour in central Africa. Burkitt noticed that the tumour had an unusual geographical distribution and set about mapping its incidence throughout Africa. He found that it occurred in a belt across central Africa, mimicking holoendemic malaria (that is, malaria occurring all the year round independent of seasons). The tumour was restricted to lowland areas where the temperature was always above 16 °C and annual rainfall exceeded 55 cm. These are the exact climatic conditions required by the mosquito vector of the malaria parasite for breeding, so based on these findings Burkitt postulated that the tumour (now known as Burkitt's lymphoma; BL) was caused by an infectious agent which was spread by the mosquito.

Epstein and his team, with the facilities to hunt for a viral cause, spent the next 2 years scanning tumour biopsies under an electron microscope for viruses using material flown in from Uganda; but without success. The breakthrough eventually came when a biopsy was delayed in transit and arrived in an unfit state for electron microscopy. Epstein cultured the cells instead. Much to everyone's surprise the cells grew, and examination of the cultures under the electron microscope showed typical herpesvirus particles. This proved to be a 'new' type of herpesvirus – later called Epstein–Barr virus (EBV). But just finding a virus in a tumour is not enough to assume a causal association. Further work found



▲ Fig. 1. Virus-associated cancers in (a) females (worldwide incidence; 19·7 % of total) and (b) males (worldwide incidence; 8·2 % of total). ■, Cervix; ■, liver; ■, vulva; ■, penis; ■, nasopharynx; ■, Burkitt's lymphoma; ■, adult T-cell leukaemia. *Dorothy Crawford*

◀ Coloured transmission electron micrograph of Epstein–Barr viruses in Burkitt's lymphoma, seen as circles with central, dark-staining DNA (red). *Dr Gopal Murti/Science Photo Library*

Table 1. Viruses associated with cancer in humans

Family	Virus	Benign disease	Tumour
Retroviridae	Human T-lymphotropic virus 1	Tropical spastic paraparesis	Adult T-cell leukaemia/lymphoma
Papillomaviridae	Human papillomaviruses	Benign warts	Cancer of cervix, skin, anus, penis
Hepadnaviridae	*Hepatitis B virus*	Hepatitis, cirrhosis	Hepatocellular cancer
Flaviviridae	*Hepatitis C virus*	Hepatitis, cirrhosis	Hepatocellular cancer, lymphoma
Herpesviridae	Kaposi's sarcoma-associated herpesvirus	Castleman's disease	Kaposi's sarcoma, Body cavity lymphoma
	Epstein–Barr virus	Infectious mononucleosis	Burkitt's lymphoma, Hodgkin's lymphoma, B lymphoproliferative disease, Nasopharyngeal carcinoma

the virus in almost 100 % of African BL, and more recently in other tumour types as well (Table 1). We now know a great deal about the way this virus transforms cells, but we still do not know the exact pathogenesis of BL. So Burkitt turned out to be right about the infectious agent causing BL, and although it is not spread by mosquitos, holoendemic malaria remains an important cofactor for tumour development.

Further discoveries

Since the 1960s five more human tumour viruses have been identified (Table 1). They belong to five different virus families, but they are all viruses which can persist in the host after the initial infection. To do this they have evolved many sophisticated strategies for evading the immune response which would otherwise clear the infection.

In all cases infection with a tumour virus is much more common than the cancer it causes, so clearly virus infection alone is not enough to cause the cancer. This is not surprising because, as outlined above, individual cells require several 'hits' before becoming cancerous. So, for each virus-associated cancer there is a series of essential events in addition to virus infection. For example, integration of the viral genome into cellular DNA occurs regularly with retroviruses but not other viruses. However, this is an essential feature of human papillomavirus- and *hepatitis B virus*-associated tumours.

It is noticeable that the incidence of many virus-associated cancers shows a marked geographical variation. This may be due to geographical restriction of the virus, as in the case of human T-lymphotrophic virus 1 which is only common in the Caribbean and Japan. Alternatively, geographical restriction may be caused by access to cofactors which are essential to tumour development. Here BL is a good example, since EBV infects over 90 % of the world's population, but the tumour is restricted to areas of the world where malaria is holoendemic.

Mechanisms of virus action

Broadly speaking there are two mechanisms by which viruses cause tumours – direct and indirect. The direct mechanism involves the virus infecting a cell and expressing its own genes. These gene products then enhance the growth potential and/or survival of that cell. Next, over time, if other growth enhancing changes occur in the same cell it may grow into a cancer, for which the virus would be an essential element but insufficient on its own.

The indirect mechanism of tumourigenesis involves the virus acting as a cofactor for the tumour but not actually being present in the tumour cells. Human immunodeficiency virus (HIV) is a good example here, since by causing severe immunosuppression it allows other viruses, such as EBV and Kaposi's sarcoma-associated herpesvirus, to act opportunistically and cause uncontrolled cell growth in the absence of the normal immune control mechanisms.

Cancer treatment and prevention

The importance of the identification of an association between viruses and various types of cancer is that it opens up new possibilities for cancer prevention and treatment. Because virus-associated cancer cells express viral antigens, they can be recognized as 'foreign' by the immune system. So vaccines can be developed which induce an effective immune response to the virus and can thereby prevent infection and consequent tumour production. Vaccines for HBV and HPV are at present being tested in clinical trials and are giving encouraging results. Also, where tumours develop in the setting of immunosuppression, the key elements of the immune response controlling the virus infection, cytotoxic T cells, can be grown in the laboratory and given to patients to prevent or treat the tumour. With these various strategies, hopefully it will not be that long before the worldwide incidence of virus-associated cancers is dramatically reduced.

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Bacteria in cancer therapy

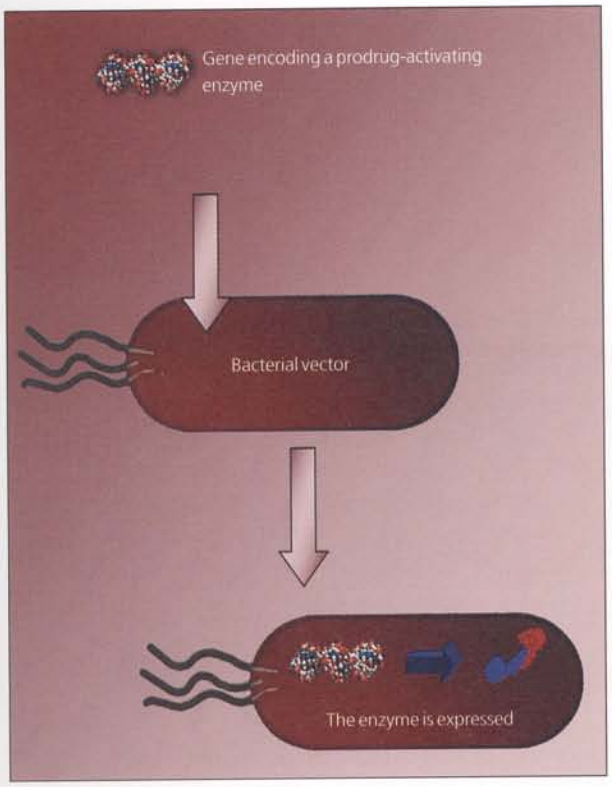
Bacteria may well have an exciting role to play in the treatment of cancer, as **Caroline Springer**, **Panos Lehouritis** and **Richard Marais** explain.

The observation that bacteria could be used as anti-cancer agents dates back 150 years. The German physicians W. Busch and F. Fehleisen separately observed that certain types of cancers regressed following accidental erysipelas (*Streptococcus pyogenes*) infections that occurred whilst patients were hospitalized. Independently, the American William Coley noticed that one of his patients suffering from neck cancer began to recover following an infection with erysipelas. Coley was so excited with this finding that he devoted his career to researching the use of bacteria for cancer therapy. Sadly, none succeeded in finding a cure for cancer due to the toxicity complications arising from these types of therapies. However, their findings provided the grounds for today's advances in this field.

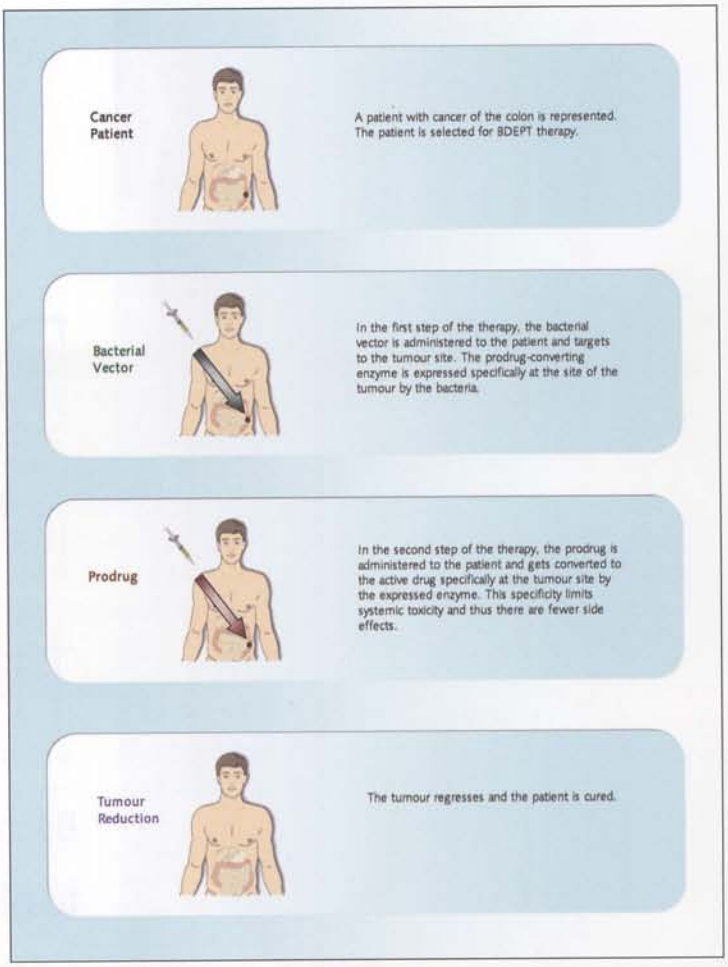
Bacteria as cancer therapy

Several decades after Coley's work, interest re-emerged in the use of bacteria to treat solid tumours. Experiments showed that pathogenic species of the anaerobic clostridia were able to proliferate preferentially within the necrotic (anaerobic) regions of tumours in animals compared to normal tissues. This resulted in tumour regression but was accompanied by acute toxicity and most animals became ill or died. Researchers then changed to a non-pathogenic strain of

◀ A female patient receiving cancer chemotherapy treatment. *Will & Deni McIntyre / Science Photo Library*



▲ Fig. 1. Construction of a BDEPT vector. A gene encoding a prodrug-converting enzyme is used to arm a bacterial gene therapy vector that has the ability to localize to tumour sites. This gene expresses the therapeutic enzyme inside the bacterial cell (The expression of the enzyme Carboxypeptidase G2 is shown as an example). *C.J. Springer*



▶ Fig. 2. A schematic of the BDEPT principle. *C.J. Springer*

Clostridium such as 'M55', showing that it was able to colonize anaerobic parts of the tumour following intravenous administration and this therapy progressed to human clinical trials. Ironically, this safer strain did not produce significant tumour regression so the trials were stopped.

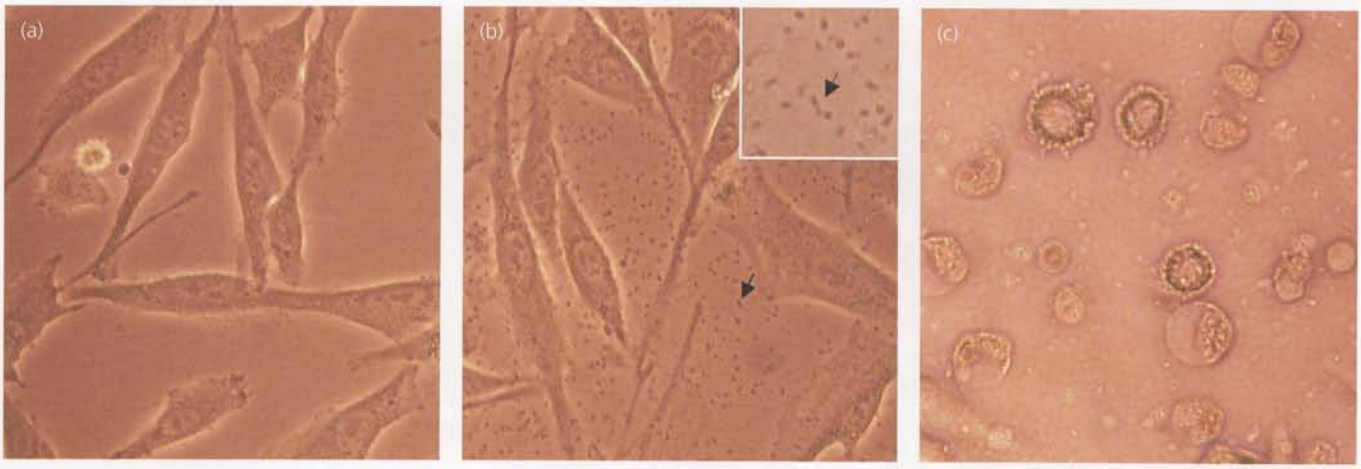
Recently, researchers have screened a number of anaerobic bacterial species (bifidobacteria, lactobacilli and pathogenic clostridia) for their ability to accumulate in experimental tumours in animals. *Clostridium novyi* was found to be the most successful candidate to demonstrate significant anti-tumour effects, but these experiments too culminated in death. A gene coding for a lethal toxin was subsequently deleted from the genome of *C. novyi*, resulting in its attenuation. Therapy experiments using the modified bacteria in combination with classical chemotherapy demonstrated phenomenal results and attracted media attention. Unfortunately, even after attenuation, the therapy was not devoid of animal deaths. *C. novyi* has now been investigated in conjunction with radiotherapy, radioimmunotherapy, and further chemotherapy in experimental tumour models demonstrating some success. Recent research into its mechanism of action revealed that it was capable of stimulating an immune response to attack and destroy the tumour. The level of inflammation induced was responsible for the animal deaths. A similar immunostimulatory mechanism of action has also been attributed to Bacillus Calmette–Guerin (BCG), the most successful bacterial agent so far, used specifically for the treatment of superficial bladder cancer.

A derivative strain of *Salmonella typhimurium* has now been developed for use in cancer treatment. Deletion of two of its genes – *msbB* and *purI* – resulted in its complete attenuation (by preventing toxic shock in animal hosts) and dependence on external sources of purine for survival. This dependence rendered the organism incapable of replicating in normal tissue such as the liver or spleen, but it was still able to grow in tumours where purine is available. This vector showed long-lasting efficacy against a broad range of experimental tumours and was even able to target metastatic lesions. Its mechanisms of tumour suppression are not entirely understood but are quite distinct from the previously described bacteria and seem to be dependent on specific genes associated with pathogenicity rather than the stimulation of the immune system.

Research in this field is growing and new strains of bacteria are being investigated as anticancer agents: *Salmonella choleraesuis*, *Vibrio cholerae*, *Listeria monocytogenes* and even *Escherichia coli* have all been shown to replicate within tumours.

Bacterially Directed Enzyme Prodrug Therapy (BDEPT)

As discussed, the major problem with using bacteria as anti-cancer agents is their toxicity at the dose required for therapeutic efficacy. Reducing the dose whilst significantly reducing the toxicity results in diminished efficacy. One approach to overcome this limitation has been to use Gene-Directed Enzyme Prodrug Therapy (GDEPT), a two-step alternative to standard chemotherapy aimed at delivering the therapeutic agent to the site of the tumour and thus limiting its unacceptable side effects. This involves 'arming' bacteria with genes encoding foreign enzymes that have the ability to convert non-toxic



▲ Fig. 3. A *Salmonella* vector expressing CPG2 is a potent anti-tumour agent. (a) Light microscopy showing tumour cells grown *in vitro*. (b) Tumour cells incubated with *Salmonella* expressing CPG2 (an individual bacterial cell is shown by the arrow). The tumour cells are not affected by the presence of bacteria. (c) In the presence of prodrug, the CPG2 enzyme, expressed by *Salmonella*, converts the prodrug into a cytotoxic agent, resulting in induction of tumour cell death, which is evident by the significant change in the morphology of the tumour cells. *C.J. Springer*

As more developments occur, it is hoped that BDEPT, an exciting new field in cancer therapy, will live up to its promise.

prodrugs to cytotoxic drugs (Fig. 1). A typical therapy regime involves intravenous administrations in two separate steps (Fig. 2). In the first step, the bacteria are administered (at safe levels) that target the tumour where they proliferate and express the therapeutic enzyme. In the second step, once the expression of the enzyme is optimal, a non-toxic prodrug is administered which is converted to the cytotoxic drug at the tumour by the expressed enzyme. This results in tumour cytotoxicity rather than systemic toxicity, leading to tumour cell death and sparing normal tissue (Fig. 2). Because the vector that is delivering the enzyme gene is a bacterium, this is also called Bacterially Directed Enzyme Prodrug Therapy (BDEPT).

Several enzyme/prodrug systems are available. Cytosine deaminase (CD), which converts 5-flurocytosine (5FC) to 5-fluorouracil (5FU), and nitroreductase (NR), which converts the prodrug CB1954 to a DNA cross-linking agent, have been tested with *Clostridium sporogenes*. Although these combinations can kill tumour cells *in vitro* and deliver high concentrations of enzymes to model tumours, to date, the results *in vivo* have been disappointing..

The *Salmonella* vector has been combined with NR and CD, and success has been observed *in vivo*, prompting a Phase I clinical trial. We have combined *Salmonella* with carboxypeptidase G2 (CPG2), an enzyme that converts a range of mustard prodrugs to DNA cross-linking agents (Fig. 3). CPG2 has been expressed in various compartments within bacterial cells and high levels of activity have been detected in tumours following *in vivo* administration, so research on this system is ongoing. It is worth noting that not all GDEPT systems will be suitable for BDEPT and many barriers will exist. For example, both the prodrug and the activated drug must be able to cross biological membranes, because the prodrug will be activated within bacterial cells and the active drug will then need to enter the tumour cells. This is unlike GDEPT, where the enzyme generally resides within the tumour cells.

BDEPT in humans is still in its infancy and there is much to learn about the targeting mechanisms of the bacteria: do enough bacteria reach the tumour compared to normal tissues; does the prodrug have access to the bacteria; is the prodrug converted to the cytotoxic drug at the tumour; and does the bacterial vector evade our immune systems? As more developments occur, it is hoped that these questions will be addressed and that BDEPT, an exciting new field in cancer therapy, will live up to its promise.

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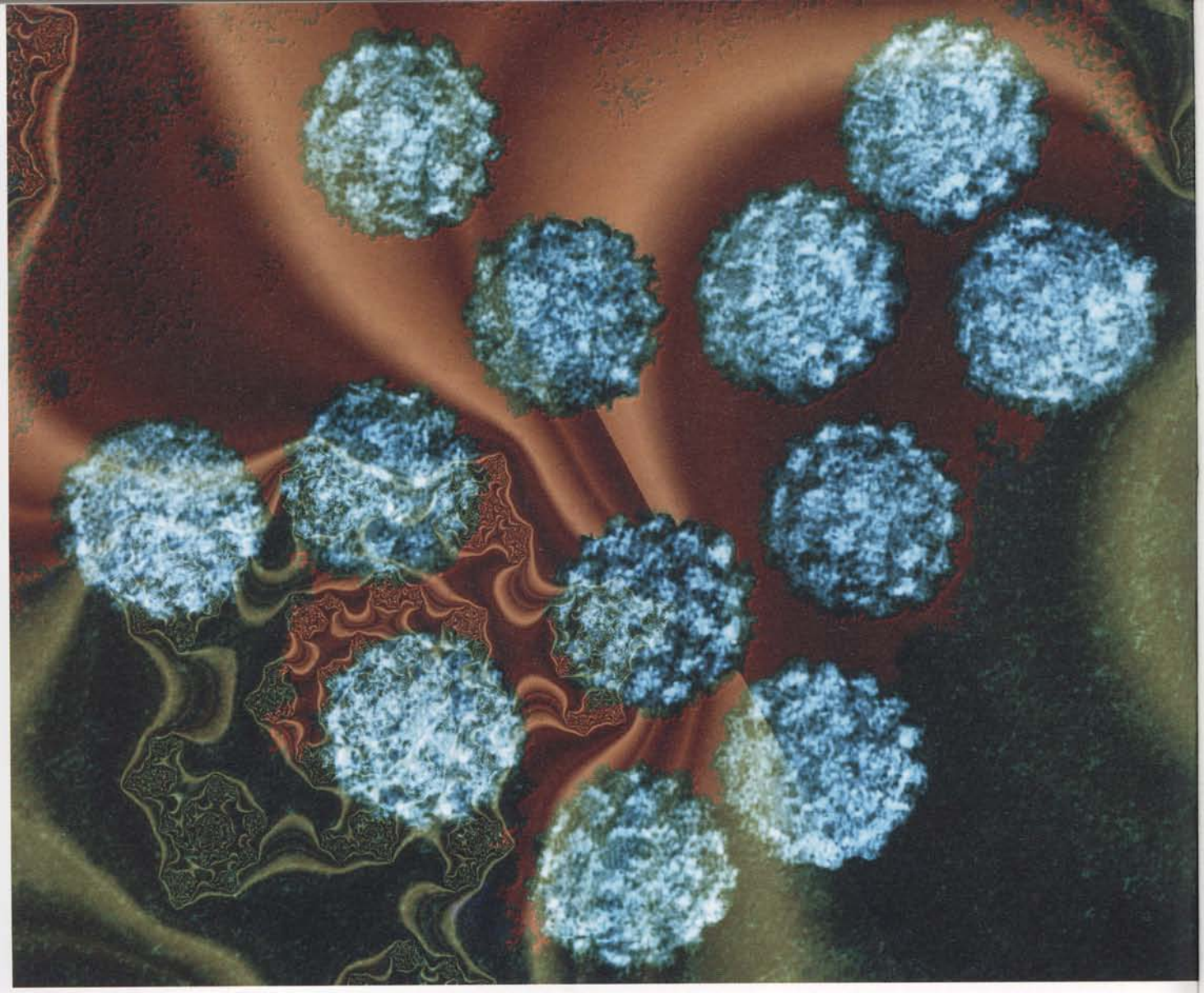


▲ Fig. 1. Coloured transmission electron micrograph of human papillomaviruses (HPV) particles. HPV form icosahedral particles that infect mucosal and cutaneous epithelial tissues. *Dr Linda Stannard/ Science Photo Library*

Papillomaviruses are responsible for a number of benign diseases, such as warts and verrucas, but they can also cause more serious conditions such as cancers of the cervix and skin. As the first effective vaccines enter the last stage of clinical trials, **Julie Burns** and **Norman Maitland** take a timely look at the role these viruses play in cancer.

Human papillomaviruses and cancer

Benign diseases such as hand warts, laryngeal warts, verrucas and numerous other skin lesions can be attributed to infection by one of the 100-plus members of the family of human papillomaviruses (HPV) (Fig. 1). These are small, double-stranded DNA viruses that infect mucosal and cutaneous epithelia through tiny cuts and abrasions that expose cells of the basal layers. The individual virus types are defined by DNA sequence homology, and the resulting phylogenetic trees can also be related to the pathologies induced by specific types (Fig. 2). Papillomaviruses have been found in most higher eukaryotes, with minimal changes to their genomic organization.

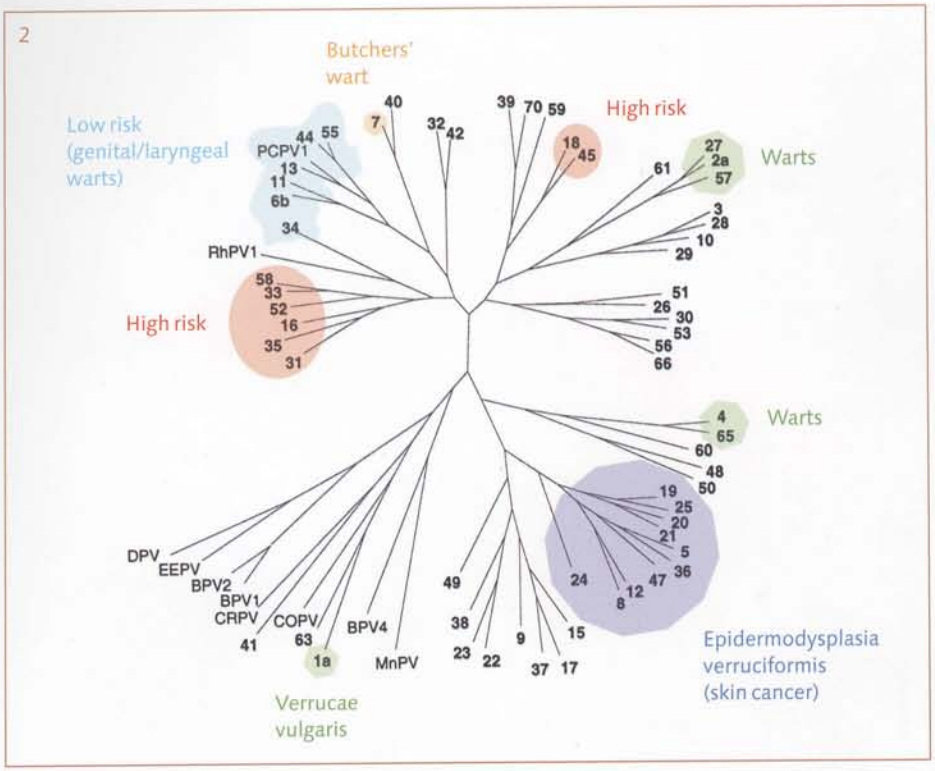
Scientific study of these small, epitheliotrophic viruses benefited from two important advances in the early 1980s: first, the cloning of HPV genomes into bacterial plasmid vectors; and second, the realization that HPV infection was linked to cervical cancer. The consequent surge in research activity indicated that over 99 % of cervical tumours contain HPV DNA, around 65 % being positive for one of the two commonest high-risk types, HPV 16 and 18. DNA sequence determination and classification led to the identification of HPV types such as 16, 18, 31, 33, etc., which were termed 'high risk for cancer induction', while others (such as HPV 6 and 11) were grouped together as 'low risk'.

HPV and human cancer

To confirm the causative link between HPV and cervical cancer, just like any infectious agent, certain criteria must be met. Essentially the basis for this was established as long ago as 1883 when Koch proposed his 'postulates' as applied to bacterial disease. During the 1970s and 1980s these postulates were modified (see Table 1a) to a form suitable for virally induced cancers (Table 1b). The mechanistic and epidemiological postulates were fulfilled in the late 1980s. It is therefore particularly appropriate to be writing this article in 2005 when we stand on the brink of fulfilling the last (and most important) of the criteria as the first effective anti-HPV vaccines are entering Phase III clinical trials.

The natural history of HPV in human cervical tissues

The majority of genital HPV infections are sexually transmitted, early after the onset of sexual activity, although there is some evidence for transmission from mother to infant. As shown in Fig. 3, infection initially results in low-grade lesions, termed cervical intraepithelial neoplasias (CIN grade I and II), which are considered pre-malignant and for the most part regress spontaneously within 1–2 years. Some infections can persist for many years and may develop into malignant tumours. Persistent high-risk HPV infection is the most



▲ Fig. 2. The papillomavirus family tree. Over 100 HPV types have been described, most causing benign hyperproliferative lesions such as warts and verrucae. About one-third of HPV types infect genital tract epithelia and a subset of these, known as high-risk types, are the causative agents of anogenital cancers, particularly cervical cancer. High-risk HPV have also been implicated in the development of non-genital cancers, with DNA found in a subset of skin and oropharyngeal malignancies. Cutaneous types (HPV 1, 2, 7, etc.) cause warts and verrucae in skin. Epidermodysplasia verruciformis-associated viruses form another large grouping typified by HPV types 5 and 8. This rare immune-suppressive disorder is characterized by keratinizing skin lesions, which can result in skin carcinomas at sun-exposed sites, depending on the HPV type present. *N.J. Maitland, modified from HPV website (http://hpv-web.lanl.gov)*

► Fig. 3. HPV and cervical cancer development. Infection of genital epithelium with a low-risk virus results in a short-term, usually self-limiting infection with benign lesions that eventually regress. High-risk HPV infections can develop to form pre-malignant CIN 1 and CIN 2 lesions. Integration of virus DNA into the genome and consequent dysregulated expression of the E6 and E7 oncogenes, together with accumulation of genetic damage, allows such lesions to progress to malignancy over a period of several years. *N.J. Maitland*

Table 1. Original and modified Koch's postulates •

(a) Koch's postulates (1883)
1. The specific organism should be shown to be present in all cases of animals suffering from a specific disease but should not be found in healthy animals.
2. The specific micro-organism should be isolated from the diseased animal and grown in pure culture on artificial laboratory media.
3. This freshly isolated micro-organism, when inoculated into a healthy laboratory animal, should cause the same disease seen in the original animal.
4. The micro-organism should be re-isolated in pure culture from the experimental infection.

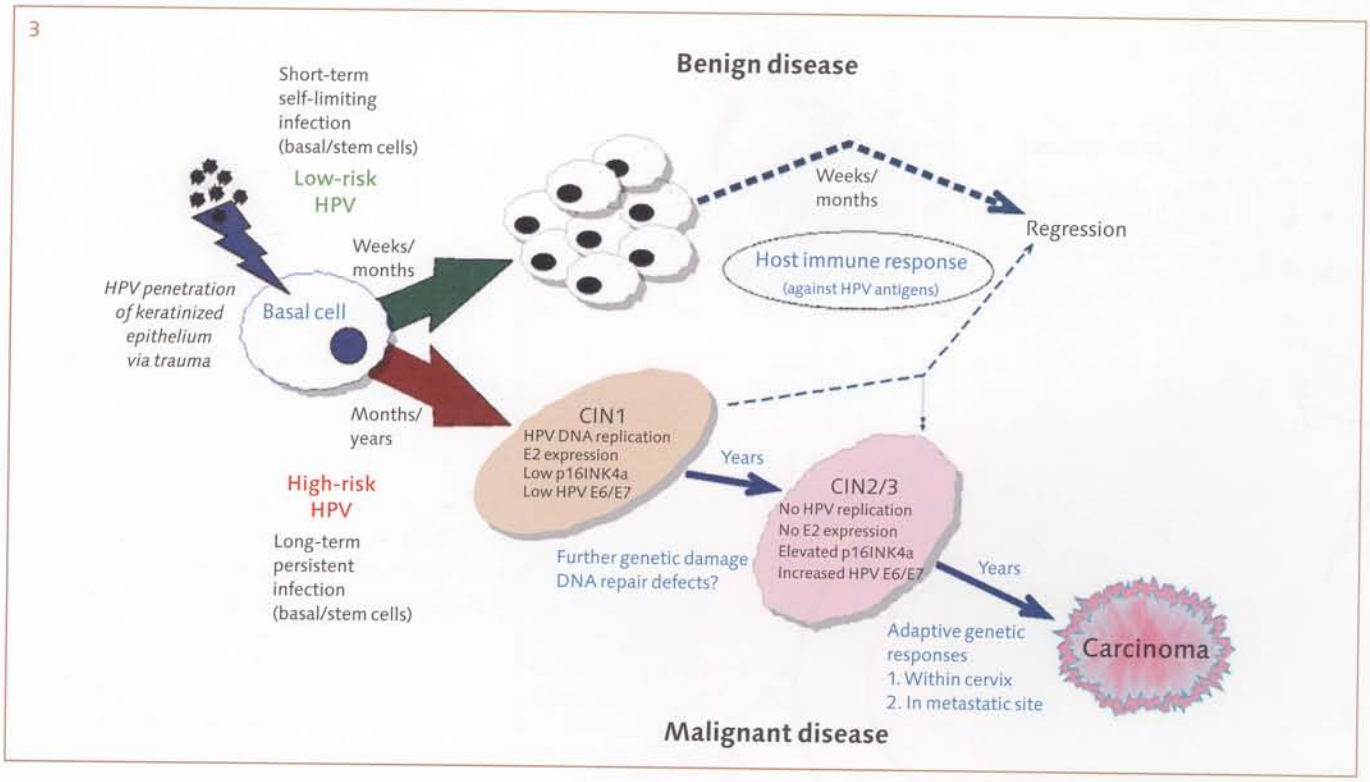
(b) Modified Koch's postulates as applied to HPV and cervical cancer
1. Do patients have evidence of a viral infection relative to the normal population?
2. Are viral genes present in the tumour cells?
3. Can the tumour be linked to the presence of an active viral gene product, e.g. an oncogene?
4. Does prevention of the infection stop the tumour e.g. by vaccination?

significant risk factor for cervical cancer, along with increasing numbers of lifetime sexual partners, infection with *Chlamydia* or HIV, immunosuppression and smoking. Worldwide, cervical cancer is the second most common form of female cancer (see Fig. 4), with around 500,000 new cases and 280,000 deaths each year, largely in the developing world. Screening based on the Papanicolou (Pap) smear-test has resulted in a decline in cervical cancer, but the annual number of cases in the UK remains stubbornly around 3,000, with an annual death rate of about 1,100.

The life cycle of HPV

HPV are obligate intracellular parasites whose life cycle is intimately linked to the differentiation of the host epithelial cell (Fig. 5a). The HPV genome encodes only eight open reading frames (Fig. 5b), hence the virus must recruit host-cell functions to maintain and replicate itself. Since the differentiating epithelial cell normally does not divide and frequently loses its nucleus after leaving the basal layer, HPV proteins have evolved to maintain their host cells in a cycling state. As a result, infected epithelia contain a much higher proportion of nucleated and dividing cells in all layers.

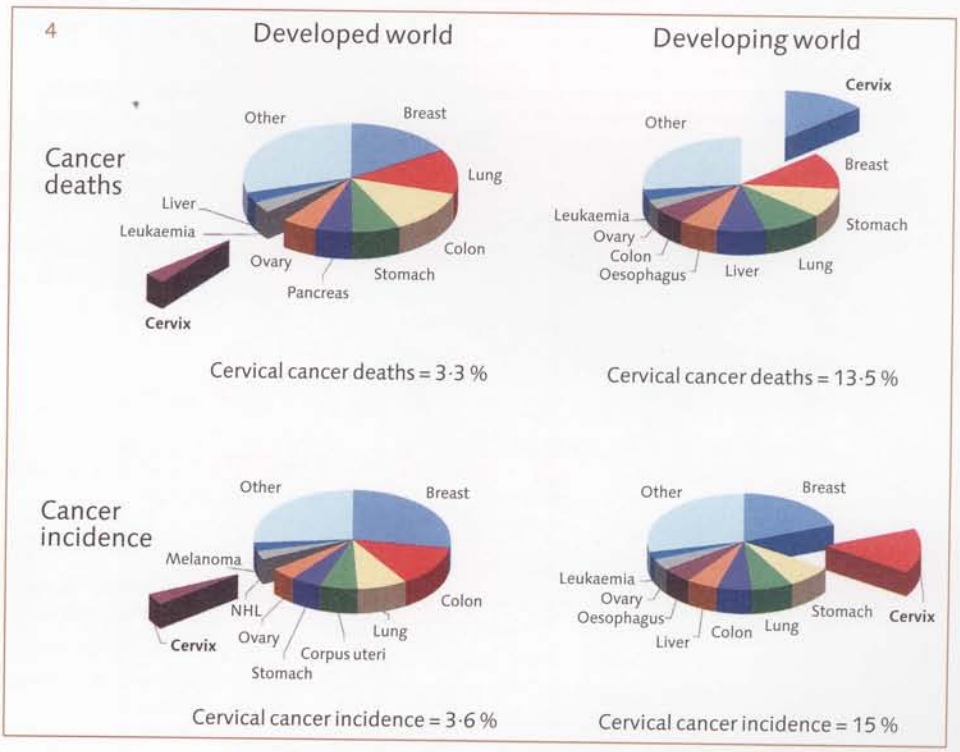
The viral proteins expressed early in HPV infection include E1, E2, E6 and E7. E1 is the viral replication protein; it binds to the viral origin of replication and directs formation of the replication initiation complex, as well as unwinding the viral DNA. E2 functions to regulate both viral replication and transcription and its loss can serve as an excellent indicator of the switch in cervical epithelium between viral replication and 'transformation' to an irrevocably pre-malignant cell. The viral oncogenes E6 and E7 have received considerable attention, mainly as a result of their ability to extend the lifespan of the host cell: useful in viral replicative strategies, but in the correct environment a pre-



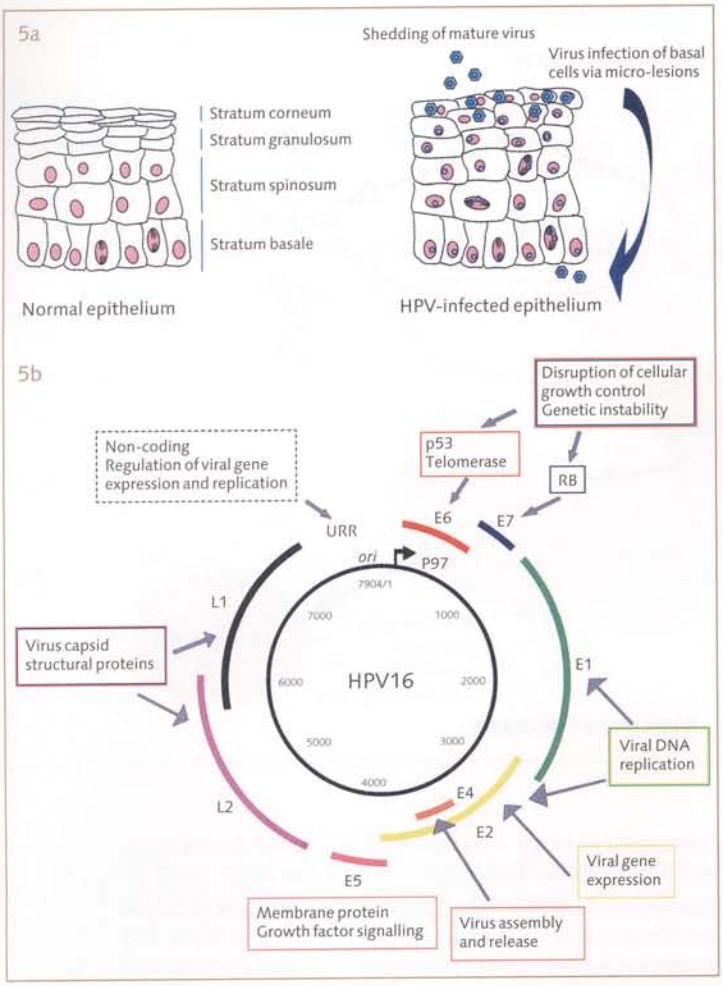
requisite for the initiation of cancer. However, the compact nature of the HPV genome determines that all of its proteins are multifunctional and interact with multiple cellular proteins.

How HPV causes cancer

A schematic outline of the two possible fates of an HPV infected cell is shown in Fig. 3. The critical role of the viral oncogenes was established more than 10 years ago: E6 has multiple activities, including the inactivation of the tumour suppressor gene p53 by ubiquitin-mediated degradation and telomerase activation (high-risk viruses only), while E7 binds to and sequesters the tumour suppressor gene pRB110, resulting in cell-cycle stimulation. The effect of these two proteins is to permit long-term unrestricted cell proliferation, with minimal checkpoint restriction to eliminate cells which might have accumulated mutations. This is ideal for the replication of HPV, as the infected host cells are induced into cycle. With high-risk HPV, a key event seems to be the integration of the virus genome into the human genome.



▶ Fig. 4. Cervical cancer incidence worldwide. A comparison of cervical cancer incidence and deaths in the developed and developing world. Screening and early treatment mean that cervical cancer is relatively rare in the developed world. The pie charts are colour-coded according to relative prevalence. In the developed world cervical carcinoma has a low incidence and almost equivalent mortality. In the developing world the relative death rate is the highest for an individual cancer, although in prevalence it ranks second. In the developing world, lack of effective screening is a major reason for the increased cancer incidence, while late detection means that cervical cancer is nearly always fatal. *N.J. Maitland, modified from IARC website (www.iarc.fr)*



▲ Fig. 5. (a) Biology of HPV. HPV replication is dependent on a differentiating epithelium. The viruses infect basal epithelial cells through micro-abrasions and the infection results in expression of early viral proteins and amplification of the virus genome, which is maintained as an episome at 50–100 copies per cell. As the host cell leaves the basal layer and terminally differentiates, progressively more virus DNA is replicated, late proteins are expressed and mature virus particles are formed, which are shed from the epithelial surface. (b) The HPV genome and protein function. The HPV genome comprises around 8,000 bases of supercoiled, circular, double-stranded DNA encoding eight overlapping genes on one strand. Early (E) genes are largely concerned with maintaining and replicating the viral genome in the host cell, while late (L) genes encode the proteins of the viral capsid. *J.E. Burns and N.J. Maitland*

Remarkably, this integration was shown to occur preferentially within the HPV E1 and E2 open reading frames, although not in a sequence-specific manner. One effect of this is the prevention of further HPV genome replication, and the stimulation of HPV oncogene expression. Over a period of years, and with the accumulation of further damage to the host-cell genome, the potential to develop as a malignant cancer is established.

The immune response

As with all exogenous infectious agents, the (human) host mounts a potent immune response against infection. In a self-limiting benign (wart) lesion the immune response eventually eliminates infected cells, which has encouraged efforts to develop vaccines against HPV. These vaccines were initially against individual viral proteins (both the capsid protein L1 and the viral oncogenes). However, vaccine efficacy was transformed by the generation of virus-like particles, which self-assembled from cloned L1 and L2 genes in a variety of host cells, including yeast, overcoming the lack of effective large-scale culture systems for HPV.

We live in exciting times for HPV prevention and treatment. The first vaccines have shown some promising results against cervical cancers in phase I trials, and in phase II trials, vaccines against HPV 16 and 18 prevented 90 % of new infections and all persistent infections. Extensive phase III trials of two commercial prophylactic vaccines are now under way.

The future

There are still problems remaining in the treatment of warts and HPV-induced cancers. For example, which patients should be vaccinated: young, sexually active/very young; female or male (or both)? Will the vaccines really show reproducible effects against all cervical cancers? Will prophylactic vaccination of previously infected patients result in selection of new HPV variants? Can those (predominantly developing) countries where cervical screening is absent and cervical cancer rates high afford to use the vaccine?

What we should not lose sight of in this new era is that the vaccine is only one weapon in the antiviral armoury and that it arose from first-rate basic science and a fundamental knowledge of the viral life cycle, which is not yet complete. Even small DNA viruses like HPV have salvage and backup pathways that have been honed over thousands of years of evolution and many replicative cycles. To close the book on supporting basic HPV science just because a vaccine is nearly here would be short-sighted indeed.

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Further reading

zur Hausen, H. (2002). Papillomaviruses and cancer: from basic studies to clinical application. *Nat Rev Cancer* **2**, 342–350.

Useful websites

International Agency for Research on Cancer
www.iarc.fr

Cancer Research UK
www.cancerresearchuk.org

International Research Grant report

The effect of PCR inhibitors in complex food samples

I was fortunate to be awarded an International Research Grant to visit the laboratory of Dr Cath Rees and Dr Christine Dodd at the Food Science department of the University of Nottingham from May to August 2004. My research centres on food safety, food-borne pathogens, diagnostics and preservation. The focus is on the development and improvement of rapid DNA methods for the detection and quantification of pathogenic bacteria in food and water.

Listeria is an important human food borne pathogen. Conventional methods to detect it in foodstuffs are generally cumbersome and time-consuming. The polymerase chain reaction (PCR) is a highly sensitive, specific and rapid method for detection of bacteria in pure cultures, but the low concentration of pathogens and the presence of PCR inhibitors in complex food samples will reduce the amplification or even block DNA synthesis. The approach that we used was to target the hlyA of *Listeria monocytogenes* to obtain 730 bp PCR product. Different pre-PCR treatments were developed to concentrate DNA or target cells, and to counteract the effect of PCR inhibitors. Different DNA polymerases, including *Taq* and *Tth* were evaluated, with different PCR buffers and different PCR facilitators.

It was found that different enrichment broths inhibited the PCR reaction when *Taq* DNA polymerase was used, but to our surprise, when we used *Tth* DNA polymerase there was no or little inhibition of the PCR reaction.

Staphylococcus aureus is a ubiquitous Gram-positive coccus, of which many strains contribute to the body's natural flora. Although not normally associated with acute disease, *S. aureus* does possess numerous potent virulence factors and, given the opportunity, can be the causative agent of serious illnesses such as osteomyelitis and endocarditis.

S. aureus is able to express a variety of extracellular toxin proteins, including toxic shock syndrome toxin 1 (TSST-1) and enterotoxins. Staphylococcal enterotoxins (SEs) encoded by the *ent* genes are the causative agents of staphylococcal food poisoning.

The aim of this part of the study was to optimize the PCR conditions for the universal forward and reverse primers to enable the reaction to be used as a universal enterotoxin detection test. The universal primers targeted conserved domains in each of the genes; therefore, the size of PCR product would be expected to be the same but with differing nucleotide sequences. To determine the number and nature of the genes present, DGGE profiles of the amplicons were produced. In this way the PCR reaction coupled with DGGE analysis had the potential for differentiating enterotoxin-positive and -negative strains of *S. aureus* and also between potential new genes in strains where no genes were previously identified.

My research visit was a fantastic experience, as it allowed me to test a few ideas in the laboratory, build collaboration and make friends. I would like to thank the SGM for awarding the grant, and Cath and Christine, as well as all the members of their labs, for making it easy for me to settle in. I would also like to acknowledge the helpful support of Dr Sara Movahedi and David Fowler.

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▲ Coloured transmission electron micrograph of *Listeria monocytogenes*. *Moredun Animal Health Ltd / Science Photo Library*

◀ The author in the lab in Nottingham. *P. Gouws*

Nobel microbes define the art of cell division

▲ Sir Paul Nurse receiving his Nobel Prize from His Majesty the King of Sweden at the Stockholm Concert Hall in 2001. *Hans Mehlin / nobelprize.org*

In 2001 Leland Hartwell, Tim Hunt and Paul Nurse were awarded the Nobel Prize in Physiology or Medicine for their discoveries of key regulators of the cell cycle (see http://nobelprize.org/medicine/laureates/2001).

Because cancer is a disease of cell proliferation that often results in cells with a varied chromosome complement, understanding the control of cell division is an important goal in cancer research. It offers significant opportunities to develop novel therapies and to make existing ones more effective.

The eukaryotic cell cycle

Unlike its prokaryotic counterpart, the principal functions of the eukaryotic cell division cycle, to first replicate then segregate the genome, are partitioned into discrete phases. Cell division is not an inevitable event, rather it is a 'conscious' step and many criteria such as cell size and nutrient status must be fulfilled before cells 'decide' to enter the cell division cycle. Once committed, cells pass through the first gap phase (G1), DNA synthesis (S) and a second gap phase (G2) before dividing in mitosis (M) (Fig. 1).

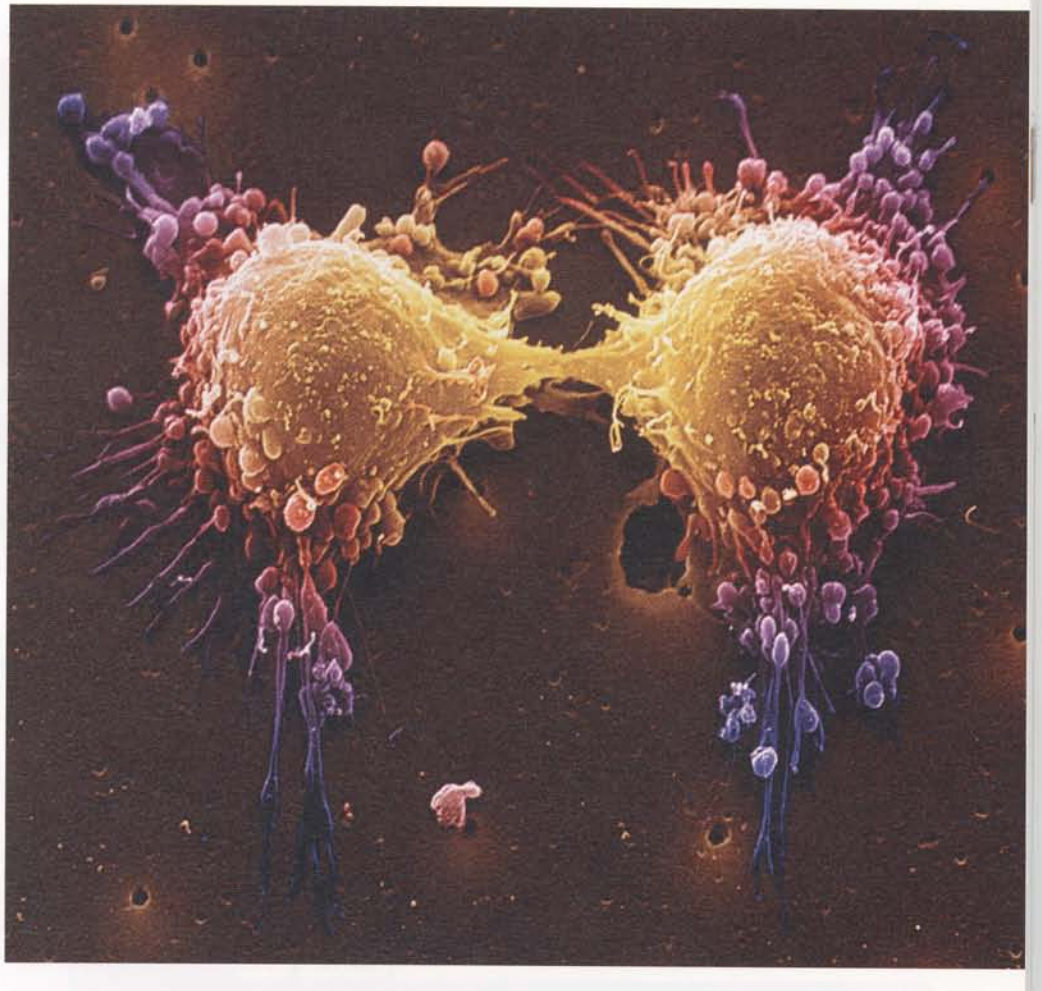
Microbes in cell-cycle research

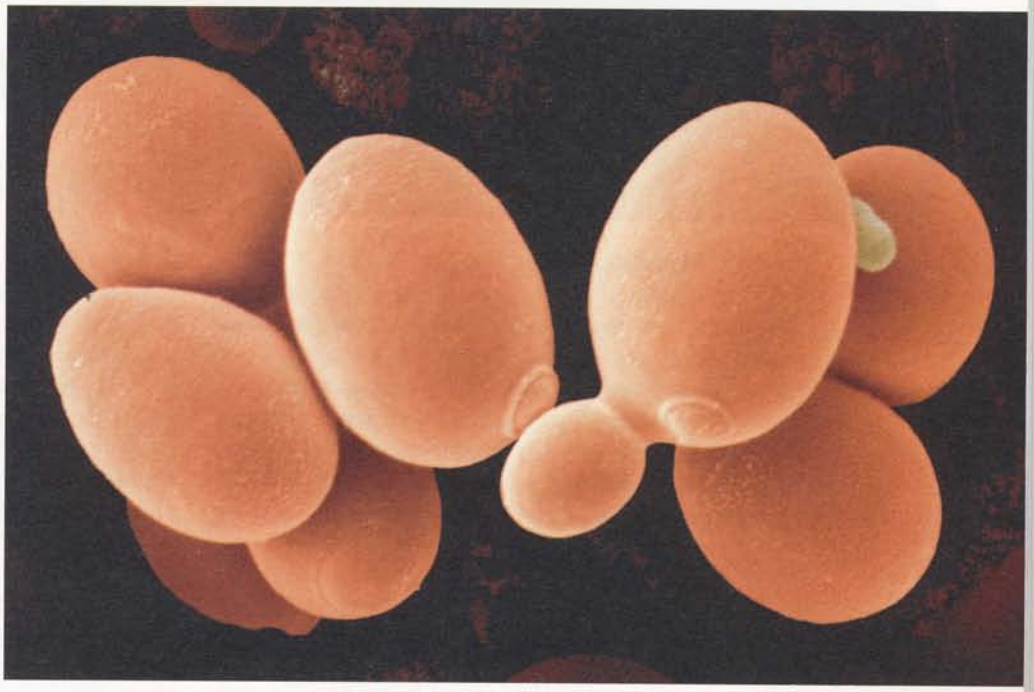
Several eukaryotic microbes have been instrumental in unlocking the secrets of the cell division cycle. Unlike the sophisticated metazoans, these model microbes, (*Tetrahymena*, *Chlamydomonas*, *Amoeba*, *Paramecium* and *Stentor*), have opted for a solitary lifestyle. As each generation in exponentially growing cultures is effectively a replica of the previous one, any variations in cell size or the time it takes to divide after particular manipulations reflect changes in cell-cycle control. Thus, the first convincing evidence for a requirement to attain a particular size prior to division came from studies of *Amoeba* by Prescott in 1956.

Physarum – the benefits of life as a giant pizza

While the solitary microbes did their bit, the more complex slime mould *Physarum polycephalum* identified some core principles that became

In the fight against cancer, understanding the control of cell division is vital. **Iain Hagan** and **Paul Nurse** show the important role of micro-organisms in unlocking the secrets of the cell division cycle.

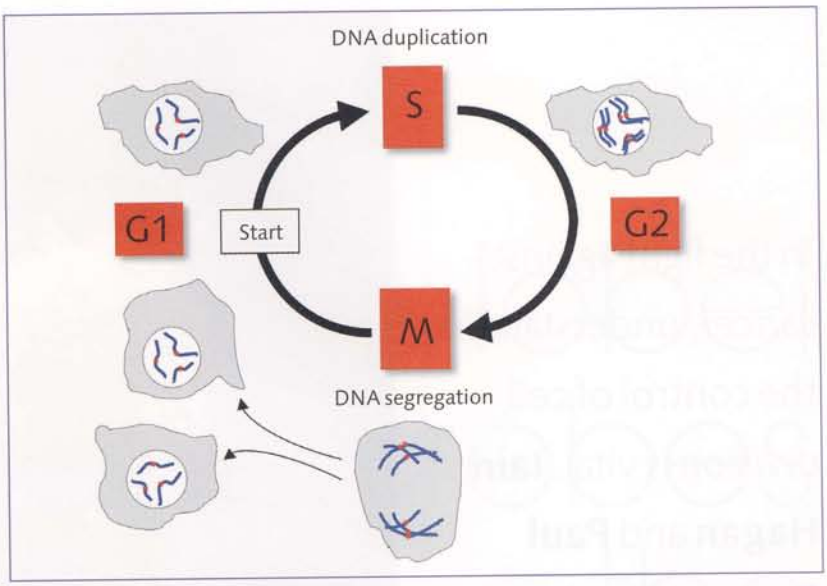




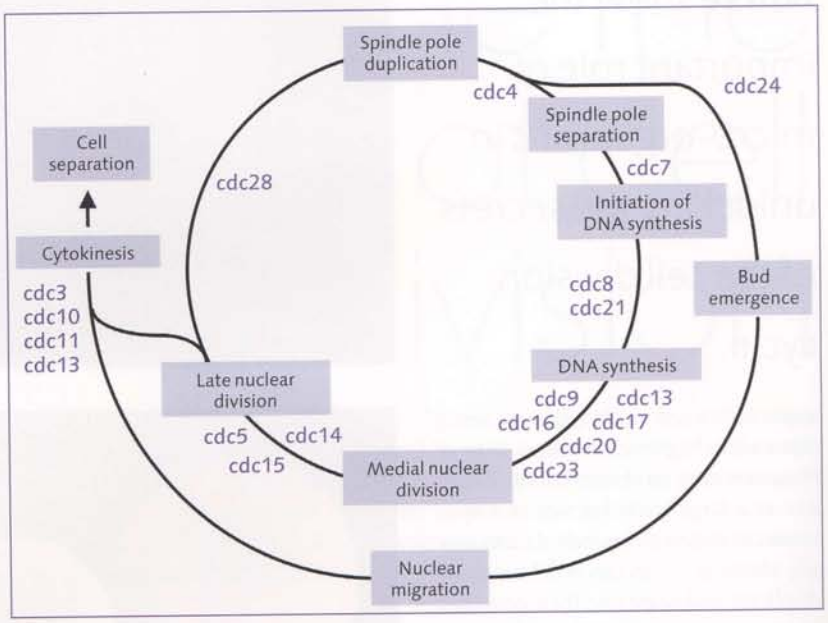
▲ Coloured scanning electron micrograph of two prostate cancer cells in the final stage of cell division (cytokinesis). During this stage the cells' cytoplasm divides. Here the cells are joined by a thin cytoplasmic bridge. *Steve Gschmeissner/ Science Photo Library*

▲ Coloured scanning electron micrograph of cells of *Saccharomyces cerevisiae*. A daughter cell can be seen budding off one of the larger mother cells. *Scimat / Science Photo Library*

ingrained in cell-cycle lore after being repeated in higher eukaryotes. One of *Physarum*'s key attributes is its ability to live as a large body known as a syncitium in which thousands of functionally identical nuclei can synchronously duplicate and segregate their genomes in a common cytoplasm, enabling sufficient material to be gathered from a single cell to study the biochemical changes that accompany cycle progression. Its second critical attribute is the ability of syncitia to fuse. Thus, syncitia of different cell-cycle phases could be merged to elucidate how strict the controls are that govern the order of cell-cycle events. The inability of an S-phase syncitium to persuade G2 nuclei to undergo a second round of replication showed that DNA replication could not be solely governed by a soluble factor. In contrast, M-phase syncitia could push G2 nuclei into mitosis. The search for this soluble M-phase-promoting factor (MPF) took Bradbury and his colleagues remarkably close to uncovering the universal controls of cell division. For they found that bathing a G2 syncitium in a histone H1 kinase preparation whose activity peaked in mitosis, pushed G2 nuclei into mitosis.



► Fig. 1. The eukaryotic cell division cycle. *I. Hagan*



► Fig. 2. Map of the budding yeast cell cycle. *I. Hagan*

The rise and rise of yeast

An emerging trend in the analysis of conserved biological problems is the eventual dominance of genetically malleable systems. The more efficient the genetics, the greater the impact of the system. Thus, analysis of mutants that displayed defects in cell-cycle progression in *Tetrahymena*, *Chlamydomonas* and *Aspergillus* has given way to the domination of the analysis of the budding yeast *Sacchromyces cerevisiae* and fission yeast *Schizosaccharomyces pombe*.

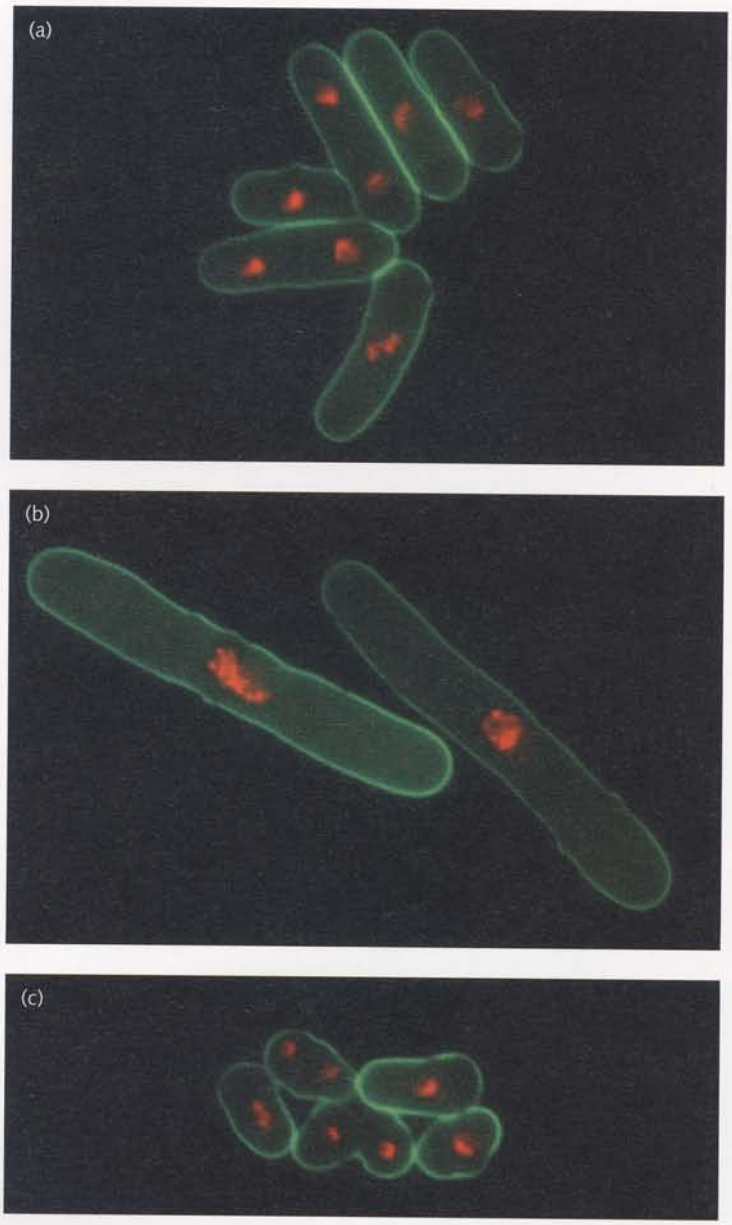
Budding yeast led the way

The seminal work of Leland Hartwell's laboratory in isolating a series of cell division cycle (cdc) mutants in the 1970s set the wheels in motion. Because genes that control cell-cycle progression will be essential for survival, he and his colleagues isolated a series of temperature-sensitive mutants that continued to grow but were unable to divide after the temperature of the culture was shifted from 25 to 37 °C. Again simple questions gave highly informative answers. The researchers reasoned that if a particular mutation results in an immediate arrest of cell division after the shift, then the number of cells that could divide after the shift would give a rough indication of where in the cell cycle that gene works. A lot of cell division after the shift indicates an 'execution point' near the beginning of the cell cycle; little cell division indicates a function towards the end of the cycle. The next reciprocal shift experiments investigated whether cells went straight into division or needed to complete a cell-cycle event (e.g. S phase) after being released from execution points. The result was a map of the cell cycle in which particular genes acted at particular times (Fig. 2). Most importantly Hartwell postulated the existence of a commitment point in G1 called 'Start'. Before Start, cells could undergo the alternative fates of mating and sporulation but once past this point they had to go all the way through the cell cycle before the chance to mate would come again. As cdc28 mutants arrested at the earliest phase of Start, Hartwell concluded that the product of the cdc28+ gene was likely to play a critical role in cell-cycle control.

wee mutants give fission yeast an edge

Growth by linear extension and division by medial fission drew Mitchison to a seminal career in the study of the *Sch. pombe* cell cycle in the early 1950s. The rationale was simple; small cells were at the beginning of the cell cycle and large cells at the end. Therefore cell length not only gave an accurate measure of the cell-cycle status of a cell, but selecting small

It is clear that microbes have advanced our understanding of cell-cycle control by many decades



► Fig. 3. Fluorescence micrographs of wild-type (a), *cdc2.33* mutant (b) and *wee1.50* mutant (c) strains of Sch. pombe. *I. Hagan*

cells gave a culture that was synchronized with respect to cell-cycle progression. The application of genetics in the mid-1970s had a further impact on cell-cycle research as a novel type emerged from the isolation of cell-cycle mutants: the wee mutant.

wee mutations made cells shorter than normal because they speeded up the rate of cell-cycle progression (Fig. 3). Classical genetic dominance relationships drew particular attention to one of the two wee loci, cdc2. The two cdc2 wee mutants were dominant and so represented a gain of function, while the loss of function mutants were classic cdc mutants. The ability of mutations in a single gene to accelerate or block cell-cycle progression put cdc2 at the heart of cell-cycle control. Strikingly, *Sac. cerevisiae* cdc28 could complement *Sch. pombe* cdc2 mutants and cdc2 acted at the two points that controlled the rate of progress through the fission yeast cell cycle: Start and the commitment to mitosis. Subsequent analysis showed that cdc2 encoded a protein kinase and that the mitosis-promoting activity of this kinase was blocked by phosphorylation in the catalytic site by a protein kinase encoded by the wee1 gene. Removal of the phosphate by the product of the cdc25 gene promoted commitment to mitosis.

wee1/cdc25 control of cdc2.cyclin B regulates mitotic commitment in all eukaryotes

The true importance of the genetic approach in yeast was realized in a period of intense activity in the late 1980s. First, a human gene that could compensate for the loss of function in *Sch. pombe* cdc2 was cloned and found to be a highly related gene – human cdc2 (Fig. 4). Almost simultaneously the purification of a mitosis-promoting factor from frog eggs showed that it was composed of frog cdc2 and a regulatory subunit called cyclin. Cyclins had become a focus of attention after Tim Hunt first showed that they were degraded once per cycle as cells divided. Furthermore, it emerged that the MPF was none other than the histone H1 kinase shown to promote mitosis in the *Physarum* syncitia 15 years previously. Thus, genetic approaches in yeast had identified the conserved means by which eukaryotes regulate commitment to mitosis. We now know that human cells possess wee1- and cdc25-related molecules, and a range of cyclin-dependent kinases (CDKs), and that these preside over all the rate-limiting steps in the human cell cycle. Molecules that play critical roles in carcinogenesis, directly or indirectly regulate these CDKs.

Budding yeast bites back – the concept of cell-cycle checkpoints

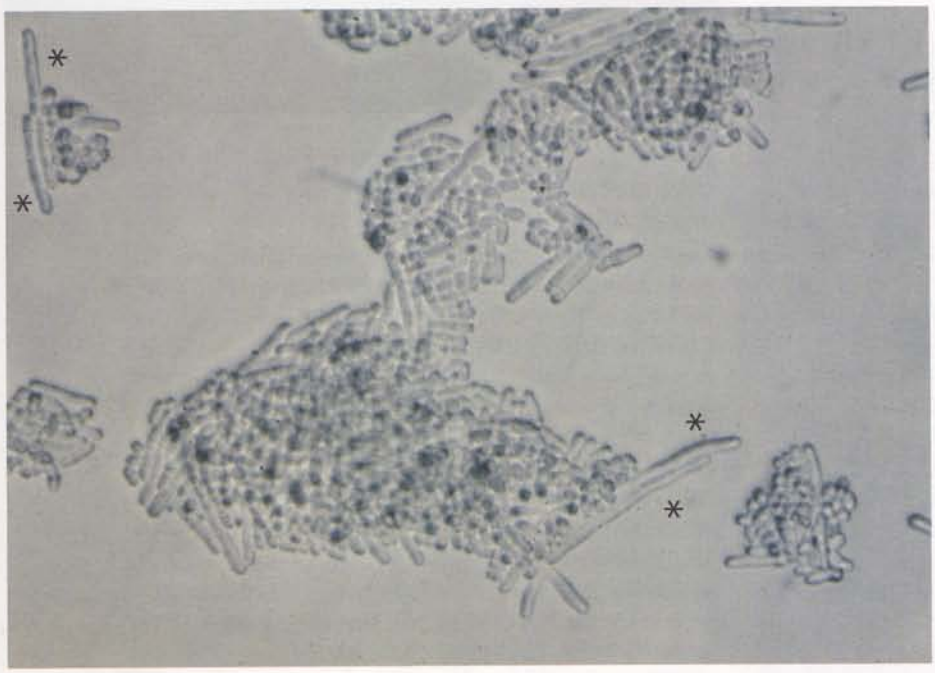
Lee Hartwell's studies of the budding yeast cell cycle were to lead him to one of the most influential contributions of the cell-cycle field to cancer research. Spurred on by numerous cases of dependency relationships, where a range of defects all arrested cell-cycle progression at similar points, Weinert and Hartwell proposed the existence of surveillance mechanisms that blocked cell division if previous cell-cycle events had not been completed or DNA integrity was compromised. They called these pathways cell-cycle checkpoints. Their elegant paper describing the DNA damage checkpoint prompted a huge body of work that makes it clear that one of the major distinctions between cancer cells and normal cells is that they are deficient in many of these check-point pathways.

Cell-cycle molecules and cancer therapy

Instead of having a reliable system of overlapping checkpoints many cancers are running on damaged or no checkpoints. This is probably why tumours are more sensitive to genotoxic drugs or ionizing radiation. The checkpoint pathways in normal cells arrest cell division in response to damage while the tumour cells continue dividing and so die. Thus not only are drugs that specifically target the checkpoint components in clinical trials at present, but ways are being sought to reinstate checkpoint controls to cancerous cells so that the abnormal genomes they possess trigger checkpoint pathways, resulting in cell-cycle arrest and eventually clearance through programmed cell death pathways.

Continuing apace

We halt our account in the early 1990s, but studies in yeast have continued to tell us how cells target specific proteins for destruction at specific cell-cycle stages, how chromosome architecture is modulated and repaired and has even got to the point where fission yeast is arguably the best system to study the mechanism underlying the mainstay of the new form of higher eukaryotic genetics – RNAi. It is clear that microbes have advanced our understanding of cell-cycle control by many decades.



▲ Fig. 4. Human cdc2 complements temperature sensitive mutations in fission yeast cdc2. The image shows colonies of fission yeast *cdc2.33* mutants that are able to divide because they carry the human *cdc2*$^{+}$ gene on a multi-copy plasmid. When they lose the plasmid they are unable to divide and so elongate (indicated by asterisks). *Reproduced with permission from Nature 327, 31–35.*

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Microbiology in the Regions report

Basidio2005

a conference on the biology of basidiomycete fungi

15 April 2005 Warwick HRI, University of Warwick

The first *Basidio* conference was held in 2003 at the then Wellesbourne site of Horticulture Research Institute (HRI); an institute with a long history of research into Basidiomycetes, especially of *Agaricus bisporus* (the cultivated mushroom). HRI has evolved into a department of the University of Warwick and *Basidio2005* was held at the new Warwick HRI. Although it was organized as a forum for the UK basidiomycete community, we were pleased to welcome international delegates from Germany, Ireland and the Netherlands. There were three main sessions each with an invited keynote speaker followed by four offered papers, plus offered poster presentations.

The meeting was opened by Dr Kerry Burton (Warwick HRI) who also gave the first keynote talk on *Sense and antisensibility – abundant natural antisense transcripts in Agaricus bisporus*. Kerry's lecture was aided by a fine set of animated slides produced by his PhD student Emilie Combet on the different mechanisms of antisense RNA production.

The second keynote was given by Professor David Read FRS (Sheffield University) who picked us all up after lunch with an excellent talk on *Basidiomycetes as mutualistic symbionts in ecosystems*. It was in this session that the co-author of this report, Dr John Thomas, gave his SGM/SfAM microbiology communication £150 prize-winning talk on *Molecular characterization of the interaction between Agaricus bisporus and Verticillium fungicola*. An additional prize of £50 was awarded to the best poster presentation by Bram Herman, a Warwick HRI/Coventry University MSc student on *Heterologous expression of mushroom lectins which inhibit in vitro proliferation of human colon cancer cells*.

The final keynote *Ecology of saprotrophic woodland basidiomycetes*, was presented by Professor Lynne Boddy (Cardiff University) who enthralled her audience with a wide-ranging and enthusiastic account of this diverse field. Lynne concluded with a statement that this warm and friendly conference had been even better than its predecessor and that delegates were looking forward to *Basidio2007*, *Basidio2009* and so on. The meeting was closed by Professor Peter Mills (Warwick HRI) and the prizes were presented by Professor Lorna Casselton FRS (SGM Council member).

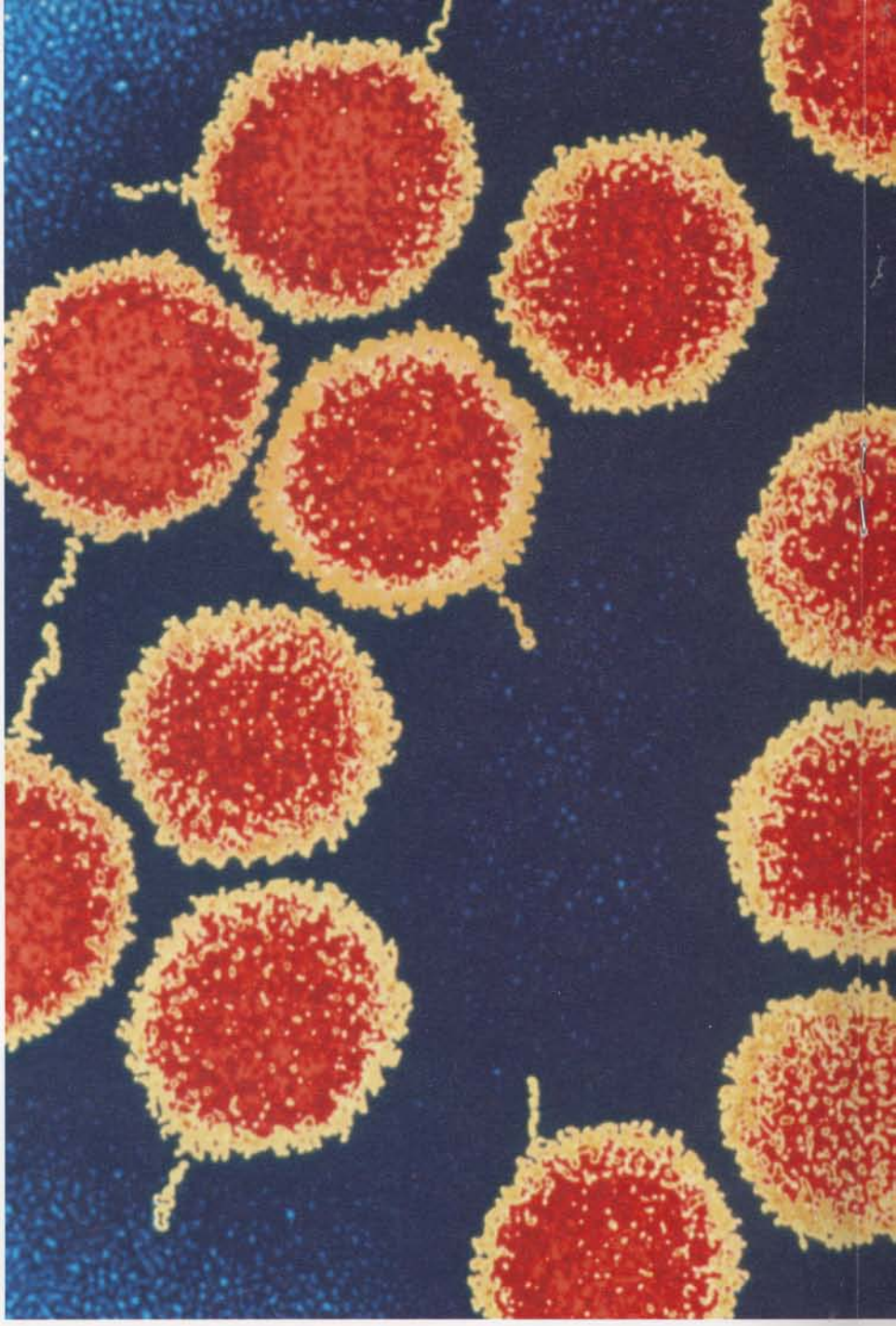
Basidio2005 would not have been possible without the generous support of the sponsoring societies (SGM, SfAM and the BMS). On behalf of the local organizing committee, the authors would like to extend a big thank you to the SGM and SfAM for the special topic meeting grant. Plans for *Basidio 2007* are underway and information will be posted on **http://www.basidio.net/**.

Dr Mike Challen and Dr D. John I. Thomas
Warwick HRI, The University of Warwick, Wellesbourne, Warwick CV35 9EF

▲ The basidiomycete *Pleurotus ostreatus* (oyster mushroom). *Steve Taylor / Science Photo Library.*

▲ Inset Dr John Thomas is presented with his prize by Professor Lorna Casselton. *John Thomas*

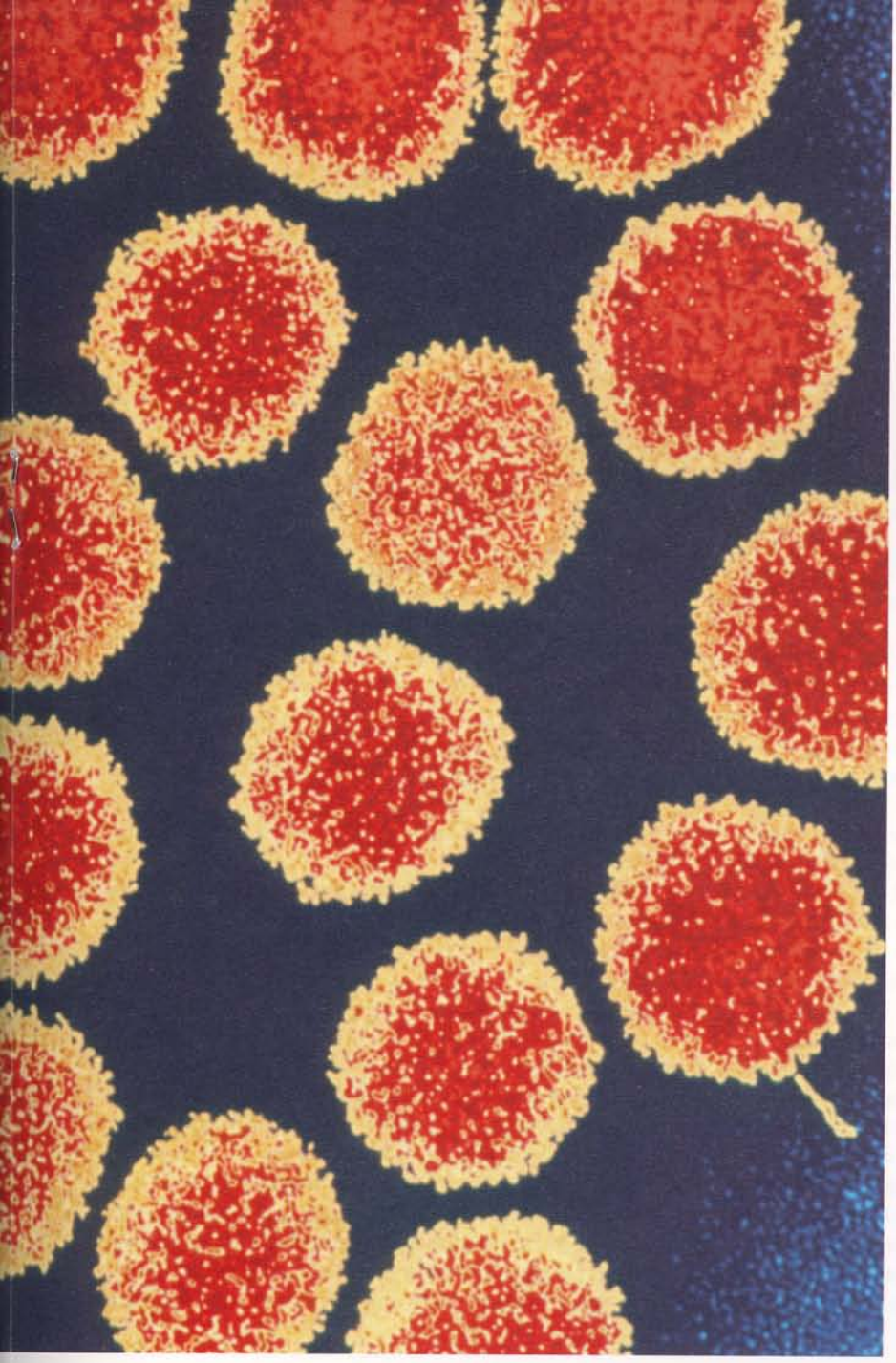
Gene therapy using viruses, commonly thought of only as agents of disease, offers great promise for the treatment of cancer as **Moira Brown** explains.



Killer into cure – oncolytic viruses

Over the last few years, a new word has crept into the vocabulary of virologists – virotherapy – the use of viruses for therapeutic purposes. In general, the word has been applied in the field of gene therapy and in the use of viruses for the treatment of cancer. This article concentrates on the latter and more specifically on oncolytic viruses.

Oncolysis describes the lysis of tumour cells by harnessing the innate ability of viruses to multiply rapidly and produce large quantities of progeny virus which results in cell death. Selectivity is achieved by modifying the virus in such a way that its replication potential is specific for tumour



◀ Coloured transmission electron micrograph of a section through recombinant adenoviruses used in gene therapy. *J.C. Revy/Science Photo Library*

cells and not for normal cells. Genetic manipulation and an intimate knowledge of virus replication strategies coupled to an understanding of at least some of the pathways involved in tumorigenesis has allowed us to do this with relative ease. Knocking out specific virulence factors is all that is required in the case of several viruses.

Early findings

The concept of viruses as therapeutic agents is not a new one. At the beginning of the last century, there were reports of cancer patients in remission from tumour progression after bouts of 'fortuitous' virus infections, such as remission of Hodgkin's lymphoma following measles virus infection. Planned human trials using viruses to treat cancer were initiated as early as the 1950s, but abandoned due to lack of selectivity and poor efficacy data. A new era dawned in the early 1990s with the report of a herpes simplex virus (HSV) engineered to replicate specifically in tumours. Since then, variants of HSV, adenovirus, *Vaccinia-virus*, *Poliovirus*, influenza virus, reovirus, *Newcastle disease virus* and vesicular stomatis virus have all been shown to have oncolytic potential in a range of tumour models and some of these viruses have been safely and successfully used in the clinic.

Approaches to therapy

Selective replication strategies have included inactivation of virulence determinants, e.g. removal of expression of ICP34.5 in HSV and the targeting of specific pathways defective in tumours, such as pRb and p53 (E1A and E1B deletion in adenovirus) and the activated Ras pathways (reovirus). These approaches have been shown to be effective in achieving tumour regression and/or eradication and prolonging survival times of tumour-bearing animals. A range of tumour models (mouse/mouse and human/mouse) have been used – glioma (a cancer of the brain), melanoma, mesothelioma (cancer of membranes lining the body cavities), ovarian carcinoma, mammary carcinoma and non-small cell lung carcinoma are just a few of the tumours which have been shown to be susceptible to oncolytic viral therapy.

Viruses on trial

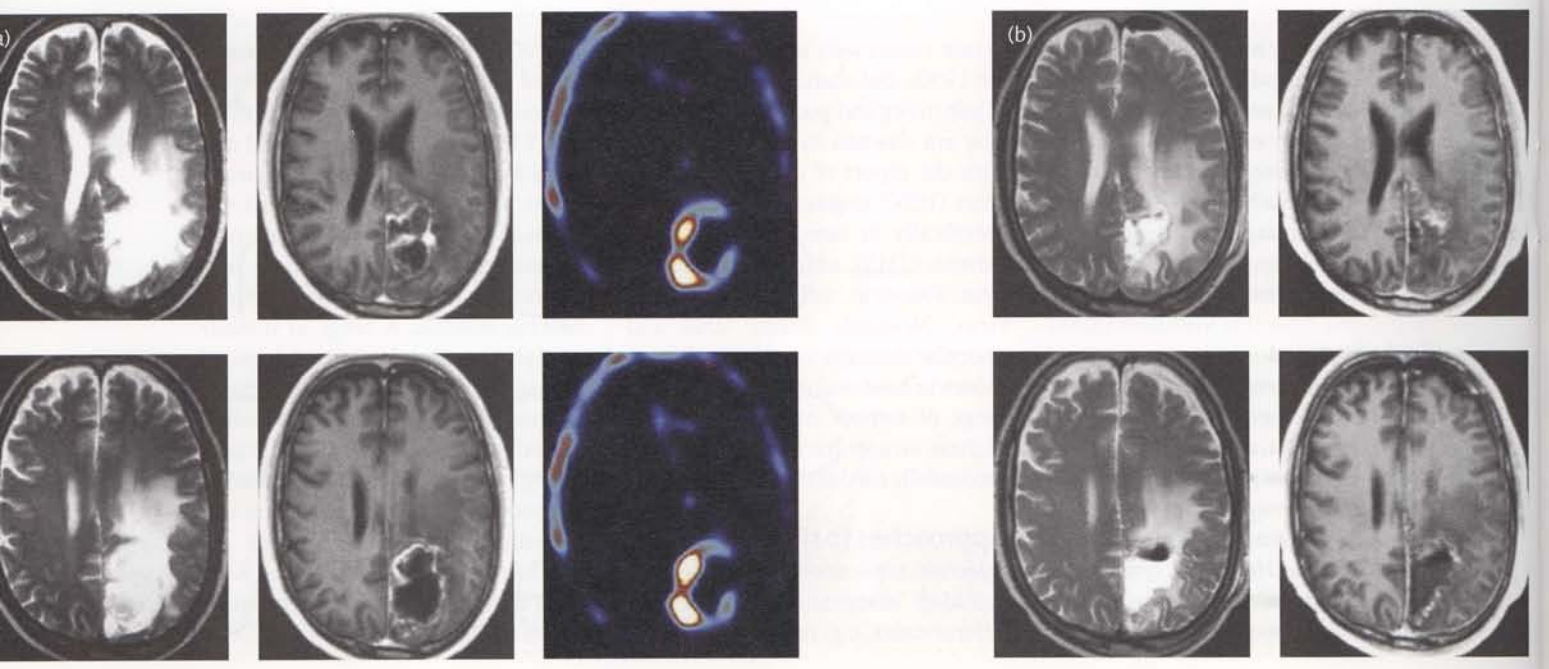
By the mid-1990s, clinical trials using oncolytic adenovirus and oncolytic HSV were underway. In the UK these trials required approval by the Department of Health, Gene Therapy Advisory Committee (GTAC) and in the USA, the equivalent committee of the Food and Drug Administration (FDA). It was no mean feat to persuade these authorities that directly injecting HSV into someone's brain should be allowed. HSV is after all a neurotropic virus which remains latent in the peripheral nervous system throughout life and on infection of the brain causes a fulminant encephalitis which, before the advent of acyclovir, was life-threatening. Those of us involved at the time had to be very convinced of the science behind the approach and also had to be either fairly brave or foolhardy! Lives could have been at risk not to say careers! Gladly, up until now all has gone well. I am unaware of any serious adverse events arising in patients from administration of oncolytic viral therapy. On the contrary these treatments have been remarkably free of side effects.

There are major ethical considerations to be taken into account in any clinical trial and one cannot take the cavalier approach of assuming that because patients have cancer, they have nothing to lose. Phase I and II clinical trials using either oncolytic adenovirus or HSV have successfully taken place in a range of cancers. In 2004, permission was granted by the European Medicines Agency (EMEA), GTAC and the Medicines and Healthcare Products Regulatory Agency (MHRA) for the most advanced trial to date using an oncolytic virus. The trial, using HSV1716 in the treatment of patients with recurrent glioma, is a pivotal efficacy trial which could lead directly to a licence and marketing approval on the basis of satisfactory results.

Viruses can be easily manipulated to act as vectors for exogenous genes and it would be good to think that several forms of anti-cancer treatment could be incorporated into one 'magic bullet'

Future challenges

Exciting times are ahead for this pioneering approach to cancer therapy. We need to show efficacy and we need to face the challenges of this type of therapy. These challenges include efficient delivery – a single direct injection into tumour is not efficient and there is a major effort now going on to find ways to deliver virus systemically and to target specific tumour types. We need to know if the immune surveillance mechanisms which most of us have to common viruses affect efficacy and if so, can they be circumvented. Viruses can be easily manipulated to act as vectors for exogenous genes and it would be good to think that several forms of anti-cancer treatment could be incorporated into one 'magic bullet'. Control and management is the current approach to cancer treatment. How much better it would be for the patient if one or more combinations of oncolytic virus



therapy, targeted chemotherapy, radiotherapy, antibody therapy and antisense therapy could be delivered as a single entity. These are the goals which we hope to achieve, but first of all we must show that oncolytic virus therapy is effective, easy to use and economically viable. The use of oncolytic viruses for the treatment of cancer is an excellent example of translation of basic laboratory findings into the clinic and exemplifies what medical research should be – use of knowledge and expertise to hopefully improve the lot of mankind.

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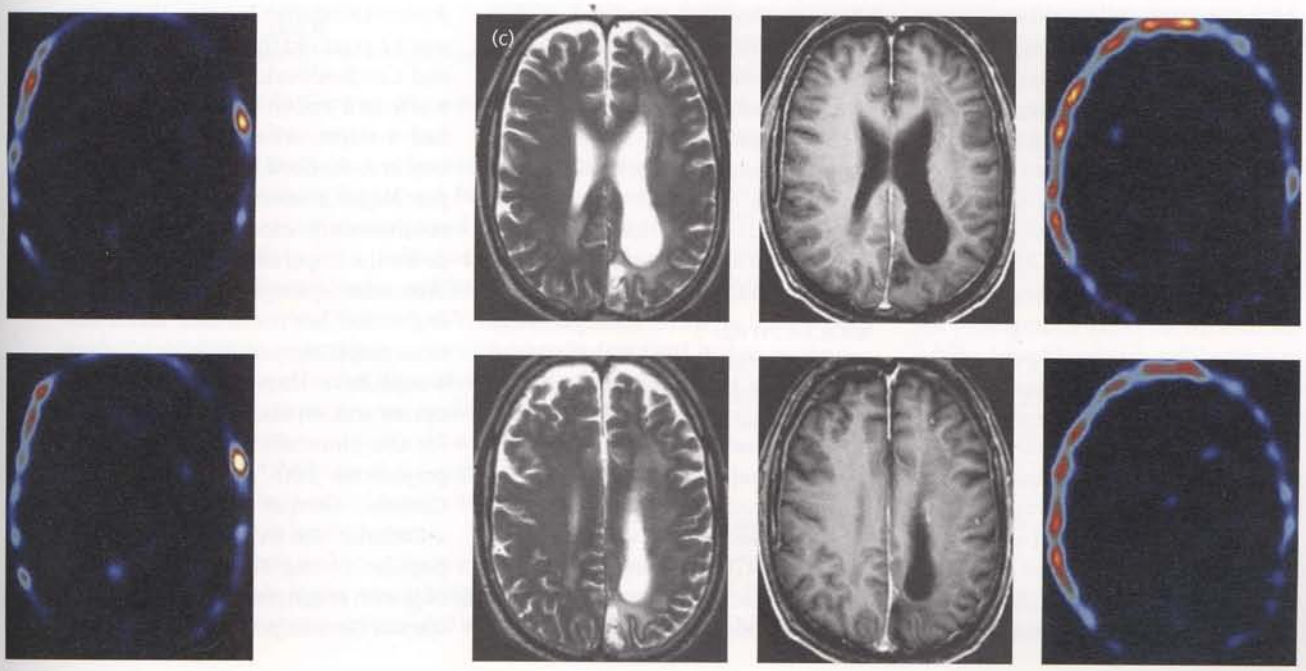


▼ Brain scans from a patient involved in the third HSV1716 trial. In each case the four scans on the left-hand side are MRI and the two on the right are SPECT (the bright area in the bottom right-hand corner of the SPECT scans is active tumour). (a) Pre-injection of HSV1716; (b) 6 weeks post-injection; (c) 22 months post-injection. *Moira Brown/Jennifer Stewart*

Two early 'general microbiologists'

Michael J. Carlile recollects two ladies, Emmy Klieneberger-Nobel and Anna Mayr-Harting, refugees from the Nazis, who made notable contributions to British microbiology.

Emmy Klieneberger-Nobel

Emmy was born in Frankfort in 1892. She studied mathematics, with botany, zoology and philosophy, in 1913–1914 at the University of Göttingen. She returned to Frankfort on the outbreak of the First World War and studied at the University from 1914 to 1917, graduating in botany with zoology and mathematics. After a period as a teacher she worked on diagnostic bacteriology and carried out research at the Frankfort Public Health Institute, producing 25 papers. She was dismissed in 1933 on the advent of the Nazis and moved to England. She succeeded in getting five nephews and nieces to England, and finally a brother, a few days before the outbreak of the Second World War, but was unsuccessful in getting her mother and sister out, and they killed themselves in 1941. Two weeks after her arrival in England she started work at the Lister Institute in Chelsea where she remained until her retirement in 1962. In 1944 she married Edmund Nobel, another refugee and a distinguished paediatrician, who died only 2 years later. In that year she became one of the founder members of the SGM.

On her arrival at the Lister Institute, the director, Dr J.C.G. Ledingham FRS, suggested that she should work on the causal organisms of pleuropneumonia in cattle and agalactia in sheep. The organism that caused bovine pleuropneumonia had been discovered at the end of the 19th century. Its size was that of a small bacterium, but it was of variable form, due to the lack of a cell wall. Other organisms with similar features were discovered and were named pleuropneumonia-like organisms (PPLOs), but proved so difficult to culture that little progress had been made by 1933. Emmy, a meticulous bench worker, soon had the cattle and sheep organisms growing on serum agar, and then extended her work to rodents, isolating two new species causing disease in rats and a third in mice. She became a leading authority on PPLOs, now known as mycoplasmas. She also observed what she at first thought were symbiotic mycoplasmas in *Streptobacillus moniliforme* cultures, and later other bacteria, and named them L organisms (L for the Lister Institute). Subsequently, it was realized that they were wall-less variants of the bacteria, and termed L-forms.

Emmy's studies extended to a wide variety of bacteria, including actinomycetes and myxococci; she published a paper on each in 1947 in the first issue of *JGM*. She also carried out work on staining bacterial nucleoids. In retirement she produced charming memoirs with a full publication list. Anna Mayr-Harting introduced me to Emmy when the latter was 65. We were attending the 1957 SGM Meeting at the Royal Institution and had gone in search of lunch. We located a Lyons restaurant and joined Emmy, already at the coffee stage. On being introduced I said 'L-forms'. Emmy, plumpish and economical in movement, conveyed the impression of a benevolent Buddha. She commented '*Some say PPLOs, some say L-forms – I'm happy either way*'.

Anna Mayr-Harting

Anna Mayr-Harting was born in Prague in 1906 when Bohemia was part of the Austro-Hungarian Empire. When she was 12 years old the Empire collapsed and Czechoslovakia was created. She was from a well-to-do background and had a nurse, who she said was '*As similar to the Good Soldier Schweik as is possible for a woman*'. When in 1918 revolutionary crowds were tearing down the Imperial Austrian Eagles in Wenceslas Square and Anna was rather frightened, her nurse said '*Isn't it nice to see people enjoying themselves*'. Anna would have then become a Czech citizen and, an alarming combination for the ethnically and ideologically prejudiced 20th century, a Czech Catholic German Jew. By religion a Catholic, she would not have been popular among the Jews, or being of Jewish origin, among the then substantial German population of Prague.

▲ Top Emmy Klieneberger-Nobel at the last scientific meeting she attended: the *2nd Congress on the Biology of Mycoplasmas* in New York in 1965. *Ruth M. Lemcke*
Bottom Anna Mayr-Harting at her retirement party in 1972. *Cliff Jeal*

Finally, being ethnically German, she would not have been a favourite of the now dominant Czechs.

Anna qualified in medicine and became active in medical microbiology. She fled from Prague with her husband and son ahead of the Nazi occupation and joined the Department of Bacteriology in Leeds in 1939. Subsequently, she moved to Bristol to become Bacteriologist and later Lecturer in the Department of Preventive Medicine, carrying out diagnostic work and continuing bacteriological research. She was a good linguist and made use of her linguistic knowledge in abstracting foreign scientific, veterinary and medical journals. When, in 1950, Bristol University established a separate Department of Bacteriology under Professor K. E. Cooper, Anna joined the department, becoming Senior Lecturer in 1964. She died in 1974, only 2 years after her retirement.

I came to know Anna well when I was at Bristol. Small and with straight white hair, she was a delightful and popular person, an entertaining conversationalist with a good sense of humour. She was keen on music, and played the trombone in the university orchestra, but perhaps her skill did not match her enthusiasm, as suggested by a tale from the Bacteriology Department humorist. At that time one of the tests in the diagnosis of gonorrhoea involved the inoculation of material into a selective liquid medium in which the causal bacterium produces gas bubbles. In the Bristol Department it seems that these bubbles were detected by an instrument that they called the gonophone, which amplified the sound made by the bubbles bursting at the surface of the liquid. The wag claimed that one day he thought that the gonophone had gone wrong, but it was only Anna practising the trombone.

Anna was a keen teacher, and in her enthusiasm for realistic exercises obtained copious material from a Bristol Hospital for her afternoon practical classes. One of her students told me that he was not enthusiastic about confrontations with a diseased kidney or material from an abscess soon after lunch. Forty years later Anna would have been in double trouble over her classes. There would have been indignation by relatives about post-mortem samples being taken without written permission, and the Health and Safety folk would have been appalled by students confronting diseased material without elaborate precautions. I did not experience Anna's post-lunch practical classes. Once, however, joining me in the University Senior Common Room for lunch, an event that I normally appreciated, she announced that she had just been translating a German forensic science article about discriminating between hanging, strangling, throttling and smothering.

I once expressed to Anna the view that the philosopher-biologist J. H. Woodger's attempt to construct a logical theoretical foundation for biology was a futile activity. Anna said that she knew Woodger and recalled how, when walking up a hill one evening, he bent over and looked at the sunset from between his legs, declaring that this would give him a view free from the usual associations. She declared that he was '*a splendid exhibit in God's Zoo*'. Anna was a fine scientist and a charming, lovable person, but the same could be said of her.

I wish to thank Janet Hurst for establishing that Klieneberger-Nobel was one of the original members of the SGM, and Barbara Costello, Biology Library, University of Bristol, for obtaining the Lancet *obituary of Anna Mayr-Harting.*

Dr M. J. Carlile
Retired microbiologist living at 42 Durleigh Road, Bridgwater TA6 7HU, UK (t 01278 447033; e mjcarlile@mjcarlile.plus.com)

Further reading

Cooper, K.E. (1974). Dr A. Mayr-Harting; Bacteriologist at Bristol. *The Times*, 10 July, p. 20.

K. E. C. (1974). Anna Josephine Mayr-Harting. *Lancet* **7873**, 177.

Klieneberger-Nobel, E. (1980). *Memoirs*. London: Academic Press.

Debate: Teaching microbiology to medical students

'This house believes that problem-orientated teaching creates better doctors'

This debate, organized by the Clinical Microbiology Group, was designed to raise awareness of the perceived neglect of microbiology in the medical curriculum and related issues associated with the recently introduced problem-based learning (PBL). In some medical schools, students' exposure to microbiology and infection is minimal and experience with PBL has been mixed. I personally have limited experience in PBL teaching, but have fought hard to protect the extensive microbiology course in Nottingham, which includes lectures, wet practical sessions and tutorials. During my search for speakers for the debate, I could not find a single medical microbiologist who was in favour of PBL, whereas among other pathologists, there was no shortage of evangelical PBL proponents. The debate was held at the recent SGM spring meeting. Professor Ian Poxton was in the chair.

For the motion

Dr Peter H. Dangerfield
Medical Educationalist,
University of Liverpool

PBL, first popularized in the 1960s, is an important reform tool for medical curricula throughout the world with an impressive track record. However, there are also clear differences between problem-solving learning and learning in ways which use problem scenarios to encourage students to engage themselves in the learning process. There are also many different opinions about what PBL actually is, although there is little doubt it should truly be viewed as a total system of learning and not isolated as a part of a programme.

PBL develops reasoning abilities, deep learning, curiosity, critical reasoning and real understanding of medical issues and conditions and contributes to communication skills.

Curriculum designers may integrate knowledge across subject boundaries. Participants in PBL become knowledge-cumulative, learning in a holistic manner, and ultimately become better clinical practitioners. While its flexibility facilitates debate about contemporary issues which reflect core knowledge, it remains vital that subject specialists, such as microbiologists, virologists and pathologists engage in the development and design of courses. Ignoring this process will lead to the loss of core content and specialty status and also contribute to diminished exposure of the specialty to undergraduate students.

PBL is an ideal system that uses new ideas to create a doctor who will have explored integrated knowledge in an adult manner, empowered to be a questioning graduate able to meet the needs of Society today. It produces a better doctor.

Dr Emyr W. Benbow
Consultant Histopathologist, University of Manchester

PBL has many advantages, though the evidence is diffuse and fragmentary. Debate has degenerated. All the perceived ills of modern medical education are blamed on PBL, whatever their provenance. Many in laboratory medicine believe the loss of traditional courses compromises recruitment of our eventual successors.

A recent study from Manchester overcomes many deficits of earlier publications, examining the performance of house officers in two successive cohorts. The former graduated from a traditional course, and the latter from a radically altered course, with severe pruning of didactic teaching in favour of PBL. Graduates and their supervisors rated the former's achievement of a broad range of skills, with significant improvements in many areas, but with an important exception – although 77·9 % of the first cohort rated themselves as '*more than quite well prepared for understanding disease processes*', only 40·1 % of the latter cohort did. This appears catastrophic to doctors and scientists in hospital laboratories, but the views of the supervisors were revealing; they had less confidence in the knowledge base of the first cohort. Personal experience as examinations tutor suggested little difference between the cohorts, so why this apparent incongruity? I think it's a major breakthrough: PBL graduates have insight into the gaps in their knowledge.

PBL is an easy target for those disaffected by modern medical education, but it is not going away in the immediate future. If we want to impress upon students that careers in laboratory medicine are worth pursuing, we must get involved.

Against the motion

Professor Mike Barer
Clinical Academic Microbiologist, University of Leicester

Arguments about PBL are just one symptom of an underlying disease in medical education. In an effort to produce patient-centred doctors who communicate well, we are in danger of producing graduates who have no systematic view of subjects that provide the rationale for key aspects of clinical practice.

The microbial world is vast and unfamiliar to students. Moreover, the intersection between the practice of medicine and this unseen world is constantly expanding and shifting. Even with conventional teaching, students need time to familiarize themselves with the different names and concepts in infection. The snapshots provided by PBL sessions cannot provide a grounding that enables students to understand the consequences of this constantly changing background.

PBL is a perfectly legitimate educational approach and is an effective way of producing an integrated approach to medical problems. It works well where students have a solid grounding that enables them to define what extra knowledge and understanding they need. It becomes ludicrous when, to address the first problem, several weeks of study are necessary.

Every large group includes students with widely divergent abilities in learning through different modalities. I believe it is madness to commit exclusively to one. In doing so we risk failing to serve some students and limiting the expectations of others regarding the range of modalities they find effective.

In my talk I drew the apparently obscure analogy between exclusive use of PBL to train doctors and the new sport of extreme ironing (http://www.extremeironing.com/). While both are inspired developments invigorating stale establishments they are also both completely mad. I urge you to iron out PBL as a monotheistic approach to medical training.

Professor Will Irving
Clinical Academic Virologist, University of Nottingham

Education in medical microbiology is in crisis. Microbiology is being squeezed out of traditional curricula, resulting in young doctors not being aware of the possibilities of a career in the subject. At the Association of Medical Microbiologists, concern has been expressed that newly qualified house officers have very little basic knowledge of microbiology and infection. Adverts for Specialist Registrar posts are attracting no more than one or two credible candidates, and vacant consultant posts are remaining unfilled due to a lack of appropriately trained individuals. The introduction of PBL courses is not going to resolve, and indeed may exacerbate, this crisis. I have no objection to medical students becoming good team players skilled in communicating with patients, and regarding their patients holistically, but I am concerned at the potential erosion of knowledge and understanding of the basic medical sciences that may arise from this style of teaching and learning. Slavery to faddism, in medical education as in all walks of life, does not provide the optimal way forward. I believe there is still a potent rationale for gathering together a large number of students in one room at a specified time, and employing one subject expert to talk to them for 45–60 minutes, explaining concepts, emphasizing what is important, and displaying an infectious enthusiasm for the subject. Long live the lecture, and the didactic teacher.

Verdict

At the end of the debate, there was enthusiastic participation from the audience, which was entirely microbiological. There was a broad consensus that a mixed approach of PBL and conventional teaching would be more useful. In the vote at the end, the only people who voted for the motion were the two pro-PBL speakers.

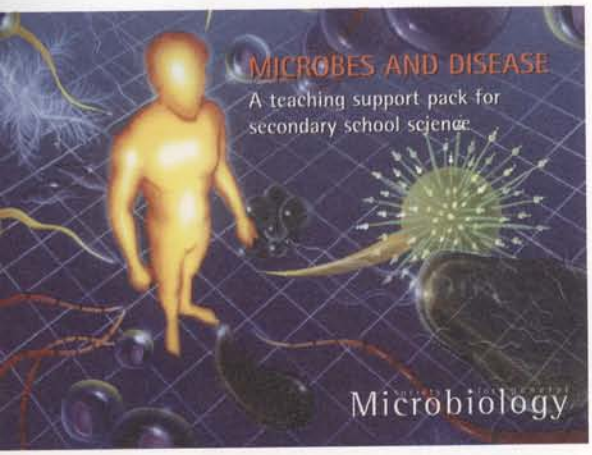
Professor Dlawer Ala'Aldeen
Clinical Academic Microbiologist, University of Nottingham and Convener of the SGM Clinical Microbiology Group (e daa@nottingham.ac.uk)

schoolzone

Schools Membership costs only £10 a year. Benefits include *Microbiology Today*, advance copies of new teaching resources and discounted fees on SGM INSET courses. To join see www.sgm.ac.uk/membership. Enquiries: education@sgm.ac.uk or go to www.microbiologyonline.org.uk

New SGM resources

To obtain any of these items, email education@sgm.ac.uk



Microbes and Disease

What's in the pack?

Two A1 colour posters showing:

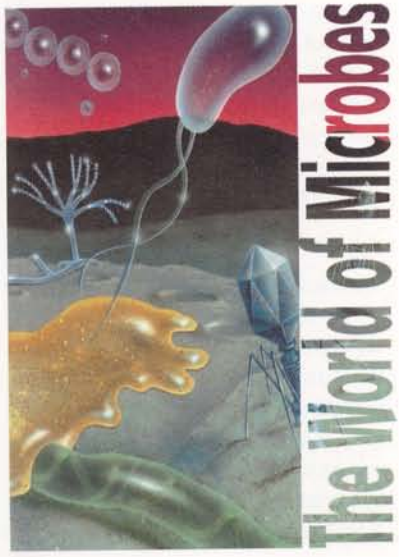
- How microbes reach us
- Defences against microbes

These posters can be used as display materials and also as a focus for teaching.

CD providing a comprehensive, full colour PowerPoint presentation on *Microbes and Disease*. The presentation comprises 63 slides and is divided into 6 main themes:

- Introduction
- Modes of transmission
- How do microbes get in?
- Defence
- Treatment
- How do microbes leave?

These themes relate to areas of the science specifications, supporting in particular Key Stages 3 and 4. However the text provides suitable background information on micro-organisms and disease, allowing it to be used as an introduction to the Microbiology and Biotechnology module in the A2 biology specifications. The presentation is fully flexible allowing teachers to modify it to suit the needs of their students.



Plants and Microbes Living in Harmony

This colourful 8-page leaflet was written for distribution to the visitors at the Chelsea Flower Show (see p. 146). It includes much information that will be of interest to schools. It focuses on beneficial plant root–microbe interactions, exploring two associations in depth:

- the role of mycorrhizas in ensuring the survival of plants
- nitrogen fixation by rhizobia in root nodules on legumes.

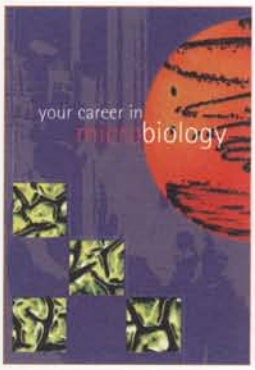
The World of Microbes

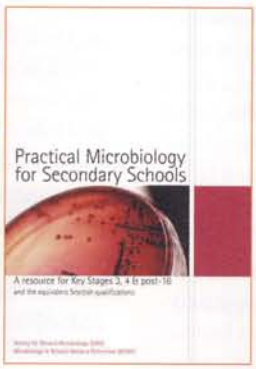
The World of Microbes pack was written for years 5/6 Key Stage 2 and supports the delivery of Unit 6B Micro-organisms in the primary science scheme of work and non-fiction literacy work. The pack contains six copies of *The World of Microbes* pupil booklet; a teacher's guide, poster and science planning sheet and normally costs £15.

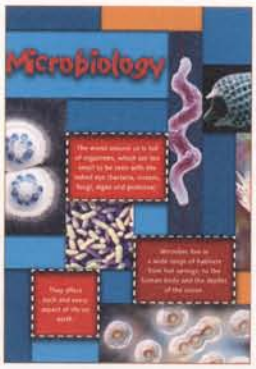
SGM Members are welcome to a complimentary pack to give to their local primary school.

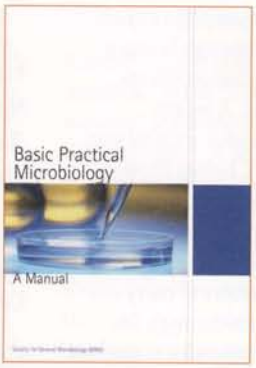
SGM education & science promotion activities

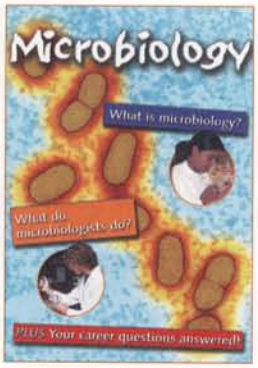
The Society takes the promotion of microbiology very seriously. It employs professionals in this field to carry out the work, in conjunction with the Education Officer and interested and enthusiastic members. The staff organize events, produce appropriate resources and deal with the enquiries that roll in daily by phone, fax, email and letter from teachers, students of all ages and the general public. Quite often they have to get out on the road and work long hours and at weekends but the team's commitment and enthusiasm rarely wanes! Here are some of the regular activities and details of the microbiology promotional material available.











EVENTS

Careers conferences

Three 1-day events are held annually on Saturdays in November at universities around the UK. These joint ventures between SGM and other bioscience societies include lectures, workshops and an exhibition plus a CV analysis service for 700–900 final year and postgraduate bioscience students each year.

Careers fairs

For many years SGM attended four to five careers fairs for schools a year with other learned societies and the Institute of Biology under the banner of *Bioscience at Work*. More recently we have joined up with the Institute of Physics and Royal Society of Chemistry to promote all areas of science on a much larger stand. This collaboration has been very successful.

Association for Science Education annual meeting

This event is attended by 4,000 science teachers from all over the world. SGM has a stand in the exhibition each year, distributing resources and advice. SGM also participates in the *Biology in the Real World* lecture programme, fielding a speaker on a cutting edge microbiological topic.

Teacher and technician training

SGM has an on-going programme of 1-day training courses in basic practical microbiology for secondary school teachers and technicians around the UK. These are delivered by John Schollar of NCBE and John Grainger of MISAC. Funding is provided for supply cover for teachers. Hundreds of people have now received training.

An extension workshop, *Microbiological Investigations for Quantitative Analysis*, has recently been developed and now runs once a year.

In July 2002 and 2004 we ran successful 5-day residential microbiology courses for 50 post-16 teachers, which were a mixture of lectures, workshops, laboratory exercises, visits and social events. SGM also organizes occasional practical workshops for teachers.

Primary school workshops

Dariel Burdass runs our popular workshops for primary school children. These involve creative activities which include making model microbes, as well as demonstrating the power of yeast to blow up balloons. These have been delivered for the Royal Institution, at the annual Albert Hall BAYSDAY, and at various other events. Dariel also runs INSET courses for PGCE students and primary school teachers on Key Stage 2 microbiology.

Science fairs, etc.

SGM participates in a wide range of events to promote the public understanding of microbiology. These include displays, practical workshops, individual talks and symposia as part of SET week, the Edinburgh Science Festival, British Association events, local science fairs, etc. A recent ambitious, but successful, exhibit was mounted at the RHS Chelsea Flower Show, which explored the interactions between beneficial microbes and garden plants. SGM also provides sponsorship for members to carry out wide-ranging activities through the PUS Fund and often provides resources and display material to support members doing outreach activities.

RESOURCES

A wide range of resources is available, most of it produced in-house and free of charge. This includes:

Posters

Classifying Microbes (wallchart and set of teachers' notes, produced in association with PCET)

Microbes & the Environment (pack of 2)

Microbes & Food (pack of 3)

Microbes & Disease (2 posters and Powerpoint presentation on CD)

Practical microbiology

Practical Microbiology for Secondary Schools (with MISAC)

Basic Practical Microbiology: A Manual

Fermenter Investigations (with NCBE – pack of student and technical guides)

Factfiles

Nitrogen Fixation and Root Nodules

Tuberculosis

Malaria

Primary

World of Microbes (Key Stage 2 pack)

Cold Wars (factfile plus an investigation)

Careers

Microbiology (careers poster and leaflet)

Your Career in Microbiology (16-page booklet)

Careers factsheets on a wide range of topics are downloadable from website.

Miscellaneous

Bioluminescence (factsheet)

Plants and Microbes Living in Harmony (booklet)

Microbiology: A Subject for Life (2 Powerpoint presentations on CD)

Websites

SGM has created and maintains two websites in-house; these separate sites, linked to the SGM site, are easily found by search engines. SGM also has resources hosted on other websites.

www.microbiologyonline.org.uk
Information on all aspects of microbiology relevant to teachers and pupils, with an interactive order form for resources and many downloadable factsheets. Also hosts and maintains the MISAC web pages.

www.biocareers.org.uk
Information on opportunities and training for microbiologists at all stages of their career, with an interactive order form for resources and many downloadable factsheets.

www.schoolscience.co.uk
Hosts the SGM database of microbiology education resources and e-source *Microbes & Food*.

www.scienceonestop.com
ASE educational website with microbiology pages written by SGM.

COMPETITIONS

SGM regularly organizes and sponsors competitions for schools.

2002 *Microbes: friend or foe* (Key Stage 2)

2003 *Poster on the body's non-specific defence mechanisms* (Key Stages 3 & 4)

2005 *MRSA: feature article in local paper* (Key Stages 3 & 4)

SCHOOLS MEMBERSHIP

This is available to all secondary schools and for only £10 a year, a named teacher receives *Microbiology Today* and benefits from discounted fees for SGM courses.

MICROBIOLOGY TODAY

A special 'Schoolzone' section in the magazine focuses on topics and news of relevance to microbiology teaching

in schools. The magazine is also distributed to the general public and opinion-formers as appropriate.

ACTIVITIES FOR YOUNGER SGM MEMBERS

SGM organizes regular events at its meetings for younger members, such as key note talks on life skills, careers, etc., followed by a buffet and drinks.

REPRESENTATION ON OUTSIDE BODIES

MISAC

SGM provides the secretariat for this umbrella body in microbiology education.

Biosciences Federation Education Group

Sue Assinder and Dariel Burdass are members and help to organize occasional colloquia on appropriate topics such as the employability of bioscience graduates.

NUCLEUS

SGM is a member of this body made up of learned societies research councils, educational charities, etc., promoting biology education; it organizes an annual symposium *Biology in the Real World* at the ASE Annual Meeting.

CONTACTS

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Sue Assinder (t 01248 382604; e s.assinder@bangor.ac.uk)

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Faye Jones (t 0118 988 1843; e f.jones@sgm.ac.uk)

Yvonne Taylor (PA to External Relations Department) (t 0118 988 1842; e y.taylor@sgm.ac.uk)

MISAC Competition 05

Education Projects Administrator **Dariel Burdass** reflects on the latest MISAC competition – *Fungi in your shopping basket*.

This year's secondary schools competition invited students to produce an illustrated A3 poster to inform the public of the importance of fungi in the production of foods, drinks and other goods in the shops. The judges looked for designs that made an immediate impact, addressed the topic clearly and used an attractive layout to hold public attention for long enough for them to learn something about the wide range of products involving fungi.

Once again the competition proved to be popular, attracting 550 entries from nearly 900 students in 80 schools. As usual there were more entries from the 11–14 age group (over 75 %) than the GCSE group.

A panel of education experts consisting of MISAC members and BMS officers carried out the judging. Many entries impressed them with their high quality of presentation, success in achieving their purpose and demonstration of a good grasp of the underlying science.

Unfortunately, some entries were eliminated from consideration for prizes as they either failed to address the aim of the competition and presented a poster on fungi in general, or they did not comply with the specified format. The judges would like to stress the importance of adhering to the rules to avoid disappointing the students who put a lot of work into such entries. It is also important that students use the correct scientific terminology, for example 'a fungus' is singular, 'fungi' is plural.

The winner of the 11–14 age range (shown above) was **Torben Kallmeier** from Royal Grammar School, High Wycombe. The winner of the GCSE age range was **Emily Oldroyd** from Durham High School.

Further details of the winners are available on the SGM education website (www.microbiologyonline.org.uk/misac). A selection of the posters will be on display at the ASE annual meeting at University of Reading (5–7 January 2006).

Every school entering the competition received a pack of microbiology teaching resources and each student was sent a certificate of entry.

MISAC wishes to express its sincere thanks to the BMS for sponsoring the 17th competition.

Next year's competition on MRSA, sponsored by SGM, asks students to create a news article for a local paper on a fictitious outbreak of MRSA at a hospital. The article needs to be of interest to and also inform the public about MRSA as well as being scientifically accurate. A briefing paper about MRSA will accompany the competition entry form which secondary schools will be able to download from **www.microbiologyonline.org.uk** at the start of the next academic year. This competition provides an excellent assessment opportunity for both Key Stage 3 and GCSE pupils.

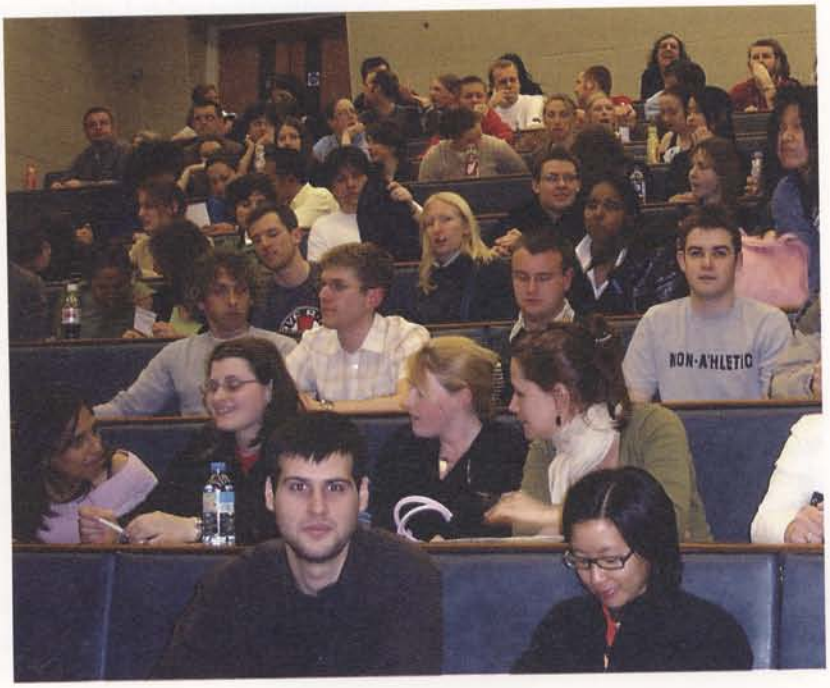
gradline

Gradline aims to inform and entertain members in the early stages of their career in microbiology. If you have any news or stories, or would like to see any topics featured, contact **Jane Westwell** (email j.westwell@sgm.ac.uk)

Surviving your PhD

The SGM PhD survival kit was neatly packaged into three excellent presentations at the Heriot-Watt meeting in April. Over 200 postgrads (and a few supervisors in the back row!) crammed into a lecture theatre to take part in a session very close to all research students' hearts. Council member Pauline Handley deftly chaired the evening which addressed three key issues that face PhD students at different stages of their training: handling the student / supervisor relationship, effective writing and defending research in the viva.

▼ Students in a lecture theatre at Heriot-Watt in April 2005 learning how to survive a PhD. *Jane Westwell*



Liz Sockett (University of Nottingham) gave a deceptively light-hearted presentation on *Managing your supervisor*. Behind the wry laughter, delegates recognized themselves and their own supervisors' characteristics. Liz offered an insight to academic scientists' research priorities and other commitments. She reminded students of their own responsibilities not only to themselves as researchers but also to their supervisors. She followed with suggestions of ways to get your supervisor to understand the way you work, tips on dealing with lab meetings and ended with some handy hints on fostering a good and professional supervisor / student relationship. Liz's talk certainly struck a chord with many delegates and sparked a number of questions from the floor.

Ian Poxton (University of Edinburgh and Editor-in-Chief of *Journal of Medical Microbiology*) guided delegates through the long process of writing-up research. He first discussed theses and reminded everyone that writing should start as early as possible in the research project (for instance materials and methods should be written as they are completed). Ian then outlined a writing timetable for the final year to help with planning and followed with some useful tips on thesis size (as concise as possible – think of your examiner!) and dealing with supervisors (don't expect them to read huge chunks of thesis in one go and give immediate feedback). He also pointed out supervisors are much happier if they don't have to correct spelling and grammar, so drafts should be as close to final as possible. After offering this advice, Ian suggested ways to hurry things along if supervisors are very slow in returning corrected chapters.

Moving on from theses, Ian then talked about publishing research in journals. He outlined the importance of this not only to supervisors but also to students' future research careers and suggested that it is best to write as the work is completed. The talk finished with some tips on writing and submitting papers to journals.

Bob Rastall (University of Reading and Food & Beverages Group Convener) rounded-off the talks by demystifying a subject that haunts most PhD students – the viva. He opened by stating that although there is no set format or style of viva, they all aim to test the candidates' abilities as independent researchers. Also, the examination process is formalized in all universities. He went on to describe examining styles and the types of questions that usually crop up. These include questions to see if students can put their work into a wider context and understand the research strategy used. Other questions probe the depth of candidates' knowledge or make them defend their position. Bob also suggested ways to deal with apparently aggressive questioning styles. The presentation ended with a set of case studies to illustrate the variety of outcomes a PhD viva can have and a reassuring list of ten top tips for success.

An intensive round of questions and answers followed the talks and continued over drinks and a buffet supper.

Jane Westwell

Postgraduate skills workshop

Employability and Career Planning for Postgraduates

11.00–13.00, 14 September 2005 – Keele University

Employability is often in the limelight, as universities are required to demonstrate how they are enhancing the employability of their graduates and postgraduates. Employability encourages students to reflect on their wider university experiences, as well as their subject knowledge, and helps them identify skills they have and areas which they need to develop.

Peter Fantom, the presenter, has more than a decade's experience as a Careers Adviser at Aberdeen University. He is also the editor of a national careers publication, *What do Graduates Do?* Peter's workshop aims to draw on experience and resources developed nationally in Scotland during 2004 and 2005.

He will give practical advice on how to set realistic and achievable career goals, how to exploit the attractiveness of generic skills to potential employers inside and outside of academia, and find out what other resources and expertise you can access on and off campus to help you achieve the career you want!

This event takes place at the SGM's autumn meeting. There are only 20 places available; bookings from Postgraduate Student Members are being taken on a first come, first served basis. Please check the box on the meeting booking form on the SGM website (www.sgm.ac.uk/meetings). A refundable charge of £5 is payable to secure a place. Delegates should also register for the meeting in the usual way.

Life Science Careers Conferences 2005

5 November	University of Bristol
19 November	University of Westminster, London
3 December	University of Newcastle

Aimed at life science under- and postgraduate students, each conference includes a range of talks on career choices and further training, plus a small exhibition by companies, organizations and higher education institutions. A CV review service is also available by prior arrangement.

SGM is involved in organizing the event and will have a stand in the exhibition.

Cost: £10, to include refreshments and lunch. Details and a booking forms are available at **www.bsf.ac.uk/careers.htm**.

hotoffthepress

Science writer **Meriel Jones** takes a look at some recent papers in SGM journals which highlight new and exciting developments in microbiological research.

First steps toward new CF treatment

Sriramulu, D.D., Lünsdorf, H. Lam, J.S. & Römling, U. (2005). Microcolony formation: a novel biofilm model of *Pseudomonas aeruginosa* for the cystic fibrosis lung. *J Med Microbiol* **54**, 667–676.

Abnormal lung sputum is one of the main problems in cystic fibrosis, leading to bacterial infection and illness. The surface of the lung is covered with a viscous liquid full of material released from cells at a much higher level than normal. Individual components appear to encourage growth of particular forms of the bacterium *Pseudomonas aeruginosa* that go on to damage the lung and can be very difficult to treat with antibiotics. Scientists have worked out that the bacterial cells grow as a biofilm, i.e. as microcolonies surrounded by a carbohydrate matrix. Therefore, one standard experimental system involves growing *P. aeruginosa* cells attached to a solid surface. However, this is not exactly the same as in a lung. One difference is that the bacterial cells attach to each other and the sputum to form a plug, rather than to the surface of lung cells. Another is that the bacteria are very tightly packed so most do not have access to oxygen. A collaboration between researchers at the Karolinska Institutet, Sweden, the GBF at Braunschweig in Germany and the University of Guelph in Canada has now shown that the composition of the sputum is much more important than anyone had guessed.

They created an artificial sputum growth medium (ASM) for *P. aeruginosa* using chemicals to match the composition of the fluid in the lungs of patients with cystic fibrosis as bacterial disease becomes established. Simply growing *P. aeruginosa* in this medium was enough to make the cells form tight clumps visible to the naked eye, rather than attaching to the surface of the culture vessel or living as single cells within the liquid. The cells grew slowly, surrounded by a matrix, just as in real sputum. The researchers discovered that every component of the ASM affected clumping by the simple procedure of leaving out each component in turn. Omitting amino acids had a particularly obvious effect, making the clumps smaller. Low levels of oxygen encouraged the cells to clump, while the fact that *P. aeruginosa* hardly grew at all without the carbohydrate-coated protein mucin suggested that this was the major energy source for the bacteria.

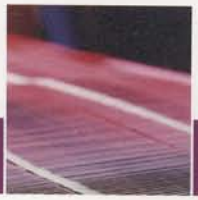
The researchers then started on the other side of the problem, to discover which genes in *P. aeruginosa* were essential for forming tight microcolonies within the artificial sputum. They tested several genes highlighted by other researchers and found that some were indeed important in the ASM. Identifying key gene products could be a first step in developing new treatments, so ASM provides a new way to test therapies against *P. aeruginosa* infections in cystic fibrosis.

Olive fly symbiosis

Capuzzo, C., Firrao, G., Mazzon, L., Squartini, A. & Girolami, V. (2005). '*Candidatus* Erwinia dacicola', a coevolved symbiotic bacterium of the olive fly *Bactrocera oleae* (Gmelin). *Int J Syst Evol Microbiol* **55**, 1641–1647.

Many insects have essential symbiotic associations with micro-organisms. There are beneficial examples where the microbe provides an essential nutrient missing from the insect's diet, and others where bacteria affect the sex ratio of the insect's offspring. In 1909, an Italian scientist, L. Petri, published a 132-page report about an hereditary symbiosis between bacteria and the olive fly (*Bactrocera oleae*). This fly is the most important pest of olive trees. The insects cannot develop from larvae to adults on olives without the bacteria and researchers have speculated that the bacteria supply missing nutrients. Adult flies contain the bacteria within a special organ called the oesophageal bulb connected to the pharynx, from which large numbers of bacteria travel to the midgut. Although Petri managed to grow bacteria taken from olive flies, he was never convinced that the numbers he obtained matched the numbers within the insects. He even speculated that the real symbiotic bacteria were viable but non-culturable.

Italian researchers at the Universities of Padua and Udine, led by Vincenzo Girolami, have re-visited this problem using molecular biological methods to detect bacterial DNA within the olive fly without needing to grow the bacteria in pure culture. They had made repeated attempts to cultivate bacteria from oesophageal bulbs and midguts on many different media without success. However, they found bacterial DNA within these organs that, although similar to DNA from the genus *Erwinia*, did not match any known species. As additional confirmation they obtained the same results for DNA extracted from olive flies collected in Bari, Liguria and Lake Garda, regions of Italy that are up to 800 km apart. The closest relative of the DNA sequence was from bacteria found on fruit and in the intestines of fruit-flies. The researchers therefore feel that it is appropriate to name the symbiotic bacteria from the olive fly '*Candidatus* Erwinia dacicola' to signify both its unculturable status and that it originates as an inhabitant of a fly from the genus *Dacus*.



In-patient evolution of the hepatitis C virus

Brown, R.J.P., Juttla, V.S., Tarr, A.W., Finnis, R., Irving, W.L., Hemsley, S., Flower, D.R., Borrow, P. & Ball, J.K. (2005). Evolutionary dynamics of hepatitis C virus envelope genes during chronic infection. *J Gen Virol* **86**, 1931–1942.

Hepatitis C virus (HCV) can cause severe liver disease, including cirrhosis and liver cancer. It is present in and transmitted through blood. Around 170 million people worldwide are at risk of disease from HCV and the number is continually increasing. Current treatments are often not effective and it can elude the immune system within the body for years before serious illness is obvious. The European Union has funded research with the aim of identifying better targets for anti-HCV therapy. As part of this, researchers at the University of Nottingham and the Edward Jenner Institute for Vaccine Research in the UK have studied how HCV changes over the years within a patient.

The researchers already knew that proteins on the surface of the virus were the key to how it fools the immune system, so they looked at the genes for these proteins. They wanted to know exactly how these changed over a number of years. To address this question they made use of samples from four patients; two of the patients had mild symptoms, but the other two had a severe and progressive disease. The patients were part of the Trent HCV Study Cohort, which consists of 2,546 people diagnosed with the virus within the 5·12 million inhabitants of the Trent region of eastern central England. The cohort was set up in 1991, when routine identification of HCV in donated blood became possible.

The researchers recorded the gene sequences of two surface proteins, E1 and E2, from HCV within each patient's samples. They cloned a total of 80 sequences, showing that each patient harboured several versions of HCV at any time. The versions of HCV in the patients also changed over the years. The team already knew that this was likely to happen and they wanted to know how the variants had evolved from each other and whether any were correlated with more serious disease. They therefore adopted methods used to work out the times at which each variant had evolved and to identify the most recent common ancestors.

This study showed that many factors affect the diversity of HCV within patients. Each patient had a unique pattern for evolution of HCV variants, without any apparent relationship to the severity of the disease. In three patients, this caused changes in the E2 protein at a location known to interact with antibodies, suggesting that these changes helped the virus to elude the immune system. Changes in further locations gave clues to specific components of the immune system involved in removing HCV and indicated interplay between attachment of the virus to human cells and escape from antibodies.

▲ False-colour SEM of *Aspergillus nidulans* conidiophores. *E. Gueho / Science Photo Library*

Fungal sex

Tsitsigiannis, D.I., Kowieski, T.M., Zarnowski, R. & Keller, N.P. (2005). Three putative oxylipin biosynthetic genes integrate sexual and asexual development in *Aspergillus nidulans*. *Microbiology* **151**, 1809–1821.

Researchers led by Nancy Keller in the USA have been studying prevention of contamination of food by mycotoxins for some years. Several fungi have a capacity to synthesize these toxic compounds in specific environmental conditions. The research has led the group into the area of signal regulation in fungal sporulation and mycotoxin production. One group of chemical signals common to both processes are oxylipins. These are involved in the switch between vegetative and reproductive growth in filamentous fungi such as *Aspergillus nidulans*. They influence the development of both the cleistothecia that contain the sexual spores and the conidophores that bear the asexual spores. *A. nidulans* normally develops asexual spores first and can then go on to produce sexual ones. However, researchers have discovered that the amount and level of different oxylipins affect the order of these processes and number of spores produced.

Two genes (*ppoA* and *ppoC*) are involved in the biosynthesis of oxylipins and the team have now identified a third gene, *ppoB*. As well as being involved in the synthesis of one type of oxylipin, the PpoB protein regulates the sporulation process. Without PpoB, the fungus produced many more asexual spores so that the ratio of asexual to sexual spores was eight-times more than normal. After several further experiments the team worked out that the PpoB protein regulated the activity of the other two *ppo* genes, affecting the balance between sexual and asexual spores.

When they combed the databases for similar DNA sequences, they found related ones in many fungi. Oxylipins could determine the timing and balance between sexual and asexual reproduction in many fungi. Some synthesize this lipid-based communication system from the lipids of the plants on which they are growing, linking back to fungal toxins in food where the story began for Nancy Keller's group.

Society gets silver medal at Chelsea for taking microbes to the gardening masses

Gardening enthusiasts at this year's RHS Chelsea Flower Show were keen to learn how microbes in the soil are helping their plants to thrive. The Society for General Microbiology's exhibit, *Plants and microbes living in harmony*, also impressed the judges, who awarded it a silver medal.

Many visitors were surprised to learn that microbes don't just cause plant diseases.

The display, designed and set up by **Dariel Burdass** and **Janet Hurst** of the External Relations Office, was situated in the Lifelong Learning section in the Great Pavilion. It explained two fascinating plant–microbe interactions: mycorrhizal fungi and rhizobial bacteria.

Gardeners were amazed to find that 90 % of land plants form mycorrhizal associations with fungi, enabling the plants to obtain vital nutrients scavenged by the fungal hyphae from the soil and providing an energy source from photosynthesis for the fungus in return. As much as 20 % of the carbon a tree obtains through photosynthesis can be transferred to its mycorrhizal fungi.

Whilst most people know that the little lumps on the roots of legumes are involved in some way in helping the plants to grow, many were not aware that the nodules are full of rhizobia bacteria that fix nitrogen from the atmosphere into ammonia, a form that the plant can use to make proteins essential for growth. In exchange the plant supplies nutrients and energy for the activities of the bacteria.

All of the plants demonstrating these associations in the Society's exhibit were those found in many British gardens – grasses, fruit trees, shrubs, ferns, herbs and vegetables – displayed against an attractive country landscape.

This was a huge undertaking by the Society and many thanks are due to the staff and also members of the SGM who helped to man the stand from 8am to 8pm each day. Their enthusiasm for the subject shone through as they talked to the many hundreds of gardeners, growers and members of the media who visited the stand over the 6 days the show was open.

More than 3,000 copies of the May issue of *Microbiology Today* focusing on 'Microbes in the Garden' and the booklet written specially for the show were distributed to the visitors, making this an enormously successful event for promoting the public understanding of microbiology.

Janet Hurst & Dariel Burdass

▲ Janet Hurst, Ron Fraser and Dariel Burdass in front of the SGM stand at the 2005 RHS Chelsea flower show, holding the silver medal awarded to the Society. *Nigel Kaye*

◀ Part of the SGM stand in the Lifelong Learning section at Chelsea. *Nigel Kaye*

◀ A page from the booklet produced for the show.

▼ A lily on display at Chelsea. *Ian Atherton*

Going with the glow

7th Wrexham Science Festival 19 March 2005

The Wrexham Science Festival was started in 1998 by a group of enthusiastic amateurs keen to convey their passion for science. Seven years on, it has grown into one of the flagship events in the science communication calendar. Each Festival culminates in 'Scientriffic', a family day of exploration and experiment centred on the North East Wales Institute for Higher Education. For the first time, this included a stand from the SGM, designed and run by postgraduate students from the School of Biological Sciences at Bangor.

It is easy to be put off getting involved in science communication activities because of concern that it will take a lot of time to organize. The SGM stand illustrated how much can be achieved with very simple ideas. The centrepiece was a display on bioluminescence, which worked well across all age groups and involved just a few plates of *Photobacterium phosphoreum* and some rolled-up tubes of black cardboard. The display was supported by the excellent SGM factsheet on *Bioluminescence* written by Janet Hurst and Faye Jones, and our bilingual 'Glow-Bug' badges were the talk of the Festival. The stand also illustrated some of the microbiological research work at Bangor, with a colourful display of bacteria involved in bioremediation of acid mine drainage and a bank of microscopes through which participants could see for themselves the diversity of microbes.

There was plenty more to excite the budding microbiologist in the other 50 or so exhibits dotted around the campus. Visitors to the display from Wrexham Maelor Hospital could learn about the role of the Biomedical Scientist and the tests used in clinical laboratories to detect pathogenic microbes, whilst the *Magic of Mushrooms* stand from the British Mycological Society illustrated the role of fungi in everyday life using models, posters and hands-on activities.

Occasions like the Wrexham Festival give the SGM the chance to reach a large and diverse audience and, if success can be judged by our hoarse voices and tired feet, we did a good job. By the end of the day, we may not have seen all of the 10,000+ visitors to Scientriffic, but it certainly felt like it!

***Sue Assinder**, Education Officer*

The World of Microbes

Portland College is a leading residential college for adults with a wide range of physical disabilities and learning difficulties. I paid a visit there in April to introduce 34 adult learners to the world of microbiology. By adapting some of the ideas in the SGM primary school booklet *The World of Microbes* we developed two 3-hour sessions of activities linked to everyday life experiences and to our curriculum. '*Practical science provides an ideal vehicle for the development and use of a wide range of transferable skills*', according to Dr D.E. Green, Director of Studies at Portland College.

We began by discussing what microbes are, the different types of micro-organism and where they are found. This provided the theme for the practical elements, which investigated the presence of microbes on the skin before and after hand washing, microbes projected into the air by coughing and microbes in the environment. For the latter task the students collected samples from around the College, including kitchen tables, telephone receivers, hand basins and a flower pot. When I returned the following week with the incubated plates, the students were able to see at that microbes were fewer in number after washing, but that most of us could make a better job of washing our hands. They also found that the hand basin in the toilets carries fewer microbes than at least one kitchen table! As student Claire Griffiths commented, '*I thought this was quite good and interesting because I've learnt something about bacteria and that I must wash my hands to get rid of germs.*'

Another activity was focused on food spoilage and investigated consequences of storing different foodstuffs at a variety of temperatures. This was linked to a tutor-led discussion of the requirements for microbial growth and simple measures to avoid food spoilage and poisoning. Examination of the foods after 1 week revealed some beautiful moulds growing on the non-refrigerated samples, and in combination with the evidence of the microbial zoos residing on most of the fingers in the room, the experiments strongly reinforced lessons on good food storage and hygiene.

▲ Portland College students busily recording the results of their experiments. *Jeff Green*

The session continued with students sampling foods from a 'microbial menu' and attempting to identify how microbes contributed to the flavour, texture and preservation of the various foods. The students were very enthusiastic about this exercise, '*I thought it was brilliant when we did experiments because we got to eat some food and store some food which went mouldy and looked gooey*', said student Jodie Birch.

We ended by discussing how our new friends, the microbes, deal with the inevitable products of our consumption down at the sewage works.

I greatly enjoyed my time with the highly motivated and enthusiastic Portland College students and staff. The feedback was very positive and is summed up by Daniel Martin: '*I thought it was fun, I enjoyed the science workshops*'.

Professor Jeffrey Green
Department of Molecular Biology and Biotechnology, University of Sheffield

Crucible:

In 2004 a group of 30 young UK scientists was given the opportunity to expand their horizons and be challenged in new ways, as participants in a pilot of the National Endowment for Science, Technology and the Arts (NESTA) Crucible scheme. They took part in a series of thematic laboratories led by world-renowned speakers. The labs were held over residential weekends and were designed to offer the scientists a unique programme of career and personal development.

During the first weekend they explored ethics in its widest sense from medical ethics to dilemma resolution. The second lab on science and politics started rather appropriately at the National Liberal Club in Westminster. It continued with talks from journalists and a scientist-turned-peer, and included a selection of workshops on management, entrepreneurship and lobbying policymakers. The group decided to respond to the Government's *Ten Year Framework on Science and Innovation*. The final lab in the beautiful surroundings of Dartington Hall in Devon featured entertaining talks on public speaking punctuated by extended sessions on drawing and painting. The organizers

▼ Neil Stokes (left) and Gail Preston (right), two of the NESTA Crucible awardees at one of the labs held in 2004. *Lee Mawdsley*

a new challenge for scientists

sought detailed feedback on the pilot that will help to develop future programmes. Several microbiologists took part.

Gail Preston, who works on plant diseases and plant growth-promoting micro-organisms at the Department of Plant Sciences, Oxford University, has long been interested in the interface of science with the arts and humanities, in science communication, and in the innate creativity of science, which the programme promised to address.

'I didn't approach the labs with a lot of preconceptions, as little information was available beforehand and the programme itself was evolving as the year progressed. The first lab provided an interesting framework in which to meet the other awardees, who were a diverse mix of postdoctoral scientists working in academia and industry. The first meeting was based around short explanations of inspirational objects. From the start, we weren't just chemists and engineers and biologists, but musicians, athletes, film-makers and voluntary workers. We were encouraged to push back the frontiers of knowledge, but to be more than just 'boffins', to think about our impact on the communities we live and work in, and to think about the role of creativity and ethics in our lives.

For myself a defining moment was in the final lab on creativity where we experimented with life drawing in different media. My drawings, paintings and sculptures in school art classes never seemed to be worth much so I wrote off the artistic side of the curriculum and focused on science, history and literature. Now in a room full of scientists and engineers I was encouraged to express myself without the constrictions of grades and technique. I loved it. I was exercising a part of my brain that I hadn't used in a long time, and yet, in some respects, the feeling was very familiar. There was the same focused energy, the same intellectual and emotional excitement that I've felt in response to a discovery that turns ideas inside out, to a challenging question or to a new solution that could solve an intractable problem.

This was, I think, what the Crucible organizers hoped to achieve. To enable scientists and engineers to step outside their routines and expectations, and to become increasingly aware of their connections to a wider world, whether to scientists in other disciplines, to politicians, to artists, to friends and family or to the next generation. For some it meant realizing that they wanted to take a new path, explore new career options. I came away feeling that I was part of a larger community, with a shared passion for exploration and innovation. I was ready to reaffirm my commitment to science, better equipped to communicate the excitement of scientific research, keen to make new interdisciplinary connections and delighted that I had taken part.'

> Crucible was designed as a new element of NESTA's existing fellowship programme, which gives tailored support to creative and innovative individuals who need the time and resources to fulfil their potential. For further details see **www.nesta.org.uk**

Neil Stokes, a microbiologist at Prolysis Ltd, a biotechnology company in Oxfordshire, does not consider creativity to be one of his strong points and he was attracted by a scheme that gave the opportunity to improve this, alongside the chance to enhance his career and personal development.

'The labs expanded my thinking in relation to the themes as I contemplated issues that I had previously not considered. In this respect Crucible met my expectations. Certain sessions were not what I had envisaged as topics that I had assumed would be covered, such as the moral implications of cloning, genetic modification or nanotechnology, were not. Crucible also achieved its objectives of offering an individual programme of career and personal development. For me the greatest benefit was the opportunity to meet and interact with scientists and engineers working in diverse fields whom I am unlikely to have encountered in my work. I enjoyed learning about these disciplines and the backgrounds and aspirations of different members of the group. Efforts to maintain this network are ongoing.

I learned little during the labs of direct relevance to my thinking about microbiology or which has impacted upon my day-to-day research. But I did not expect to and I do not think this is what NESTA intended. However, I enjoyed the opportunity to explore issues outside the laboratory, yet still related to science and research in the wider sense. For other microbiologists interested in considering the implications of their research or understanding the interface between science, art and the humanities this is a programme unlike any other and I would recommend it.'

***Janet Hurst**, External Relations Office*

reviews

If you would like your name to be added to our database of book reviewers, please complete the book reviewer interests form on the SGM website. A classified compendium of reviews from 1996 to the present is also available on the website.

Microbial Inhabitants of Humans: Their Ecology and Role in Health and Disease

By M. Wilson
Published by Cambridge University Press (2005)
£35.00 pp. 455
ISBN 0-52184-158-5

This is indeed an 'advanced textbook' as claimed, in terms of the amount and depth of content. However, the content is presented in an accessible style, with each chapter laid out in a consistent format, facilitating comparison across the different body sites which are described. Illustrations are black and white, with simple illustrations and several micrographs (some a little dark).

The book provides an up-to-date, comprehensive review of current knowledge concerning the normal flora of a range of different sites on the body, and associated endogenous infections. Information on the better studied areas such as the mouth, gut, reproductive system, respiratory system and skin is presented in chapters of 50 pages or so, with the eye and the urinary tract being covered in shorter chapters of around 20 pages. Each chapter finishes with suggested reading – books and reviews/papers, the latter being particularly up-to-date. It is especially welcome to read current reviews on the oral flora, where the literature is huge and rapidly developing.

The introductory chapter provides an excellent overview of the subject, encompassing the community nature of the microbial populations at these differing sites. The concept of the biofilm, and the varied biofilm structures which might be encountered in the body are noted (although not highlighted as a chapter subheading). Communication, and the difficulties of characterization of the indigenous microbiota are addressed.

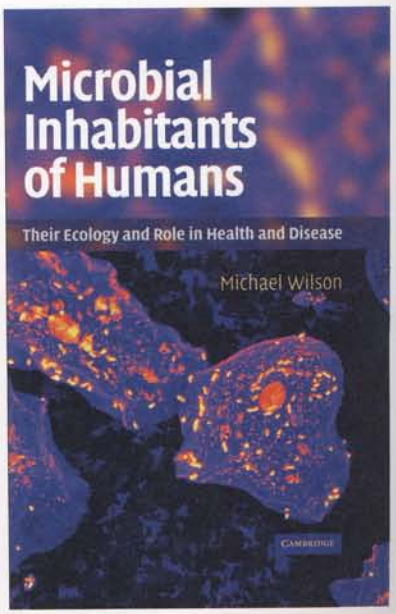
The last two chapters focus on the important 'role of the indigenous microbiota in maintaining human health'. The sections describing colonization resistance and the effect of micro-organisms on host development set the scene for the final 'manipulation of the indigenous microbiota' in order to maintain, or return to – or create – a population consistent with health. Pre- and pro-biotics, inhibition of adhesion, disruption of biofilm, replacement therapy and 'modification of the environment' (primarily focused on the elimination of anaerobes) are outlined rather broadly, but the information provides interesting snapshots of some current approaches.

I particularly liked the 'host' factors which were introduced in the indigenous flora chapters. Brief aspects of human physiology are included where necessary, describing the environmental factors that influence the microbiology. The changes occurring as the host ages are noted: an important aspect to be considered in our increasingly ageing population. The impact of medical devices and associated infections is also addressed, with examples provided in appropriate chapters (e.g. contact lenses – the eye; implants – the skin).

Each chapter provides an excellent introduction to the site of interest, and would rapidly acquaint the novice – for example a postgraduate student about to embark on a research project in the area. I would certainly recommend the book for library purchase, or purchase by academics teaching and/or engaged in research in the area. The book might be too detailed and too costly for use as an undergraduate text. I cannot imagine a course which would concern itself with predominantly non-pathogenic micro-organisms – we always emphasize that the overwhelming majority of micro-organisms are at least not harmful, and are often beneficial, but rarely do we have the luxury of spending time addressing this in class. It is therefore particularly enjoyable to find a book which does just this.

Indeed, all the world is here – in this case Planet Human – in terms of many of the concepts which the modern microbiologist needs to address. The human body provides an excellent example of a range of environments where enormous numbers of micro-organisms cohabit. Interesting facts serve to reinforce the significance of our indigenous flora. The book pays suitable tribute to the 1·25 kg of prokaryote load that each of us carries, and provides a timely reminder of how much remains to be learnt about the normal human flora.

***Joanna Verran**, Manchester Metropolitan University*



Organelles, Genomes and Eukaryote Phylogeny: An Evolutionary Synthesis in the Age of Genomics. The Systematics Association Special Volume Series 68

Edited by R.P. Hirt & D.S. Horner
Published by CRC Press (2004)
US$99.95 pp. 400
ISBN 0-41529-904-7

This is an outstanding set of reviews that effectively captures the current state of play in eukaryote relationships. The current situation is a real quagmire with an unmanageably large set of contradictory proposals floating out there in the literature, so this book is a boon to those seeking to follow the debate from the sidelines and especially for those who teach eukaryotic microbiology. It has been let down by poor quality typesetting and plate reproduction. Nevertheless, I will be using this as a set text for teaching at MSc level. No-one expects that this is the last word, of course, and achieving resolution between these groups will no doubt cause more taxonomic mayhem, but I thoroughly recommend it to those who want to know where we're currently heading in eukaryotic evolution and systematics.

***Dave Roberts**, The Natural History Museum*

Introduction to Biodeterioration: Second Edition

By D. Allsopp, K. Seal & C. Gaylarde
Published by Cambridge University Press (2004)
£19.99 pp. 252
ISBN 0-52152-887-9

The most remarkable thing about this book is that it is an interesting read!

Whether the reader is familiar with the various aspects of biodeterioration or is merely curious about this applied science, the information presented is quite fascinating. It makes one aware of the impact of biodeterioration in industry, commerce and in everyday life.

The book, intended as an introduction to biodeterioration, reviews and updates, with the authority of experience, the areas traditionally associated with the biodeterioration of materials of economic importance. An entirely new area included is that of molecular biology. The treatment of nucleic acid analysis techniques is dealt with succinctly and the contribution of these techniques is appraised.

The control of biodeterioration will be a useful reference for many who work in industry.

For teachers, the book is a welcome ally and for those concerned with the preservation and conservation of materials, it is essential reading.

***Glyn Morton**, University of Central Lancashire*

Principles and Practice of Infectious Diseases Online: Sixth Edition

By G.L. Mandell, J.E. Bennett & R. Dolin
Published by Churchill Livingstone/ Elsevier Science Ltd (2005)
£199.00 CD-ROM
ISBN 0-44306-672-8

Principles and Practice of Infectious Diseases is regarded by many as the leading textbook in the field of infectious disease. However, the size and weight of the regular book edition is now such that use of a reinforced bookshelf seems a sensible precaution. The availability of an on-line edition with an accompanying CD-ROM containing all the images that complement the text is thus very welcome. Individual sections or chapters can be easily accessed using either the contents menu or search facility. There are also useful links that allow the authors and titles of references cited in the text to be viewed directly. Given that even the best textbooks become quickly out-of-date, the inclusion of regular content updates is an invaluable feature.

Although expensive, this is a superb resource that should be available, at least at departmental or library level, for all those with an interest in infectious disease.

***Alan Johnson**, Institute for Animal Health*

Reviews on the web

Reviews of the following books are available on the website at www.sgm.ac.uk/pubs/micro_today/reviews.cfm

Genetically Modified Crops: Their Development, Uses, and Risks

Brucella: *Molecular and Cellular Biology*

Yersinia: *Molecular and Cellular Biology*

Microbial Diversity: Form and Function in Prokaryotes

Strict and Facultative Anaerobes: Medical and Environmental Aspects

Freshwater Microbiology: Biodiversity and Dynamic Interactions of Microorganisms in the Aquatic Environment

Colonization of Mucosal Surfaces

Campylobacter: *Molecular and Cellular Biology*

Bacteriophages: Biology and Applications

The Microbe–Host Interface in Respiratory Tract Infections

RNA Interference Technology: From Basic Science to Drug Development

Agrobacterium tumefaciens: *From Plant Pathology to Biotechnology*

Microbial Enzymes and Biotransformations

Microbial Processes and Products

Medical Biomethods Handbook

Immunology in Plant Health and its Impact on Food Safety

Biotechnology & Genetic Engineering Reviews: Volume 21

Scientific Integrity: Text and Cases in Responsible Conduct of Research, Third Edition

Biodefense: Principles and Pathogens

obituaries

Ernest Frederick Gale FRS

15.07.**1914**–07.03.**2005**

SGM Member (1944–1990)
Honorary Member (1990–2005)
Meetings Secretary (1956–1958)
International Representative (1965–1967)
President (1967–1969)

▲ Ernest Gale

Ernest Gale, who has died at the age of 90, was Professor of Chemical Microbiology in the University of Cambridge from 1960 to 1981. He made a significant contribution to the Society's activities during its early years. His major contribution to microbiology was in emphasizing the chemical and enzymatic basis of microbial activities, at a time when many cellular components and biochemicals were ill-defined. These ideas were published in 1947 in the ground-breaking book *The Chemical Activities of Bacteria*.

Ernest Gale spent 50 years in Cambridge, completing a degree in Natural Sciences (Biochemistry) in 1936 and then a PhD in the Department of Biochemistry under the direction of the late Dr Marjory Stephenson, FRS, for studies on the adaptation of sugar-metabolizing enzymes in *Escherichia coli* and factors that influence the deamination of amino acids. This research led to a rapid and accurate method of estimating free amino acids, which in turn facilitated the study of the movement of amino acids into and out of bacterial cells. Using naturally occurring amino acid auxotrophic strains of *Staphylococcus aureus*, Gale showed that large intracellular concentrations of amino acids could be accumulated. He was to be one of the first to use radiolabelled amino acids, although his initial approach to Amersham to supply him with ^{14}C-amino acids was met by resistance and the comment that there would be no general scientific market for such esoteric products!

During the 1950s, Gale worked on the involvement of RNA in the incorporation of amino acids into protein, using an *in vitro* system from *S. aureus*. At that time it was not possible to separate the different types of RNA, but he clearly saw that there were separate effects, that a labile form of RNA was involved in enzyme induction and synthesis, and moreover that DNA was responsible for organizing the involvement of RNA in protein synthesis. With hindsight it is possible to distinguish the effects of mRNA and tRNA in the results obtained, but at the time they were part of a lively controversy, which Gale eventually left to the likes of Crick and Monod to resolve.

Instead, Gale turned his attentions to the mode of action of antibiotics, triggered not only by the finding that penicillin altered bacterial permeability to amino acids and inhibited synthesis of the cell wall, but also to an incident during World War II. Gale had received from ICI a small sample of penicillin, but before he could use it for laboratory experiments he received an emotional call from a clinical colleague to help a nurse dying of a staphylococcal infection. Administration of the penicillin produced a dramatic improvement in the nurse's condition, but there was insufficient to continue treatment and she died. This experience had a profound effect on Gale who devoted the rest of his scientific career to the study of antibiotics. A succession of PhD students and academic visitors to his laboratories investigated a wide range of antibiotics, shedding light not only on their modes of action, but also the elucidation of basic aspects of bacterial metabolism. His book *The Molecular Basis of Antibiotic Action* remains a classic text. Later he turned his attention to antifungal antibiotics, particularly the polyenes and mechanisms of resistance.

The originality of Gale's research and its significance for the development of microbiology was marked by the award of the ScD degree in 1947 and his election as a Fellow of The Royal Society in 1953. In 1948 he became Director of the Medical Research Council Unit for Chemical Microbiology or 'Microbiology Unit' (MBU) within the Department of Biochemistry, and in 1960 the University of Cambridge created a personal Chair of Chemical Microbiology for him. Although he was an efficient administrator, Gale was happiest doing research and even when he was Acting Head of the Biochemistry Department he still set aside a day when he could work uninterruptedly in the laboratory. He held many distinguished lectureships at home and abroad and travelled widely giving lectures in Russia, the USA and Australia. He sat on several national and international committees, including the International Union of Biochemistry Commission on Enzymes from 1957 to 1961.

Ernest Gale was an excellent lecturer and laboratory teacher, his great enthusiasm for his subject being very evident. He was much involved in the radical reorganization of undergraduate

teaching at Cambridge in the mid-60s that saw the replacement of older disciplines with the newer concepts of biology of cells. As a PhD supervisor, his aim was to instil an ability in his students to think for themselves: he had an uncanny ability to guide whilst allowing the freedom to explore without undue pressure. Testimony to the success of his approach is found in the large number of his students who have become leaders in academia and industry.

Ernest Gale retired in 1983, moving from Cambridge to live in Salcombe, Devon, where regular family holidays had been spent for many years. In retirement he spent his time walking and swimming, reading thrillers not scientific papers, and developing his considerable skills as a wood carver. The last years of his life were blighted by virtually complete loss of memory, and were spent in London closer to his family. To the end he remained unassuming and dignified, somewhat ironically succumbing to a pneumonia that not even the antibiotics that he had studied for a professional lifetime could cure.

Nick Russell
Imperial College London

Carlos Hormaeche

24.12.**1940**–29.03.**2005**

SGM Member (1981–2005)

Group Convener (1991–1994)

Council (1994–1999)

Professor Carlos Hormaeche has died in a microlight aeroplane crash in Uruguay. He was born in Montevideo, Uruguay. He was multi-talented and could have pursued several careers, but his calling to research was greatest. He graduated from medical school in Montevideo and developed a strong and active interest in microbiology.

▲ Carlos Hormaeche

In 1981, I had just finished my second year as an undergraduate at Cambridge when we first met. I turned up to work in his laboratory as a prelude to my final year Part II research project, to discover that he was about to go off on a month's vacation. He outlined the project, told me that I could use the laboratory while he was away and then let me get on with it. That was the way it was in Cambridge in those days: no spoon-feeding! With this and subsequent experiences during my PhD with Carlos he liberated me intellectually and personally, an experience I think many have shared, and for which I will always be grateful.

Carlos was very supportive and kind to his students, but expected respect for the science and absolute engagement in the problem in return. He was a supreme enthusiast and had an amazing and encyclopaedic knowledge of bacterial pathogenesis, being able to quote chapter and verse from the literature and taking it as a personal affront if he could not remember the page numbers from a reference from 20 years ago. This professional pride rubbed off on those around him, and has always inspired me to try to be similarly engaged.

Carlos, his wife Raquel Demarco, and their young son Sebastian, arrived in Cambridge in 1972 where Carlos started a PhD in the laboratory of Professor Robin Coombs. When the military dictatorship took power in Uruguay in 1973, Carlos and Raquel courageously protested at the injustices taking place, and took active roles in human rights organizations. The family thus had to remain in England until the late 1980s when democracy was restored in Uruguay.

After his PhD he continued his research on immunity to *Salmonella* infections in the Department of Pathology. He became a University Demonstrator and in 1980 was awarded a Lectureship in the same department. In 1994 Carlos became Professor and Head of the Department of Microbiology at the University of Newcastle. He re-organized and re-invigorated this Department leading to it moving from a 2 to a 5* rating in the RAE of 2001.

His science focused on infectious disease and mainly on mechanisms of resistance and immunity to *Salmonella* infection. His PhD thesis unravelled for the first time the complexities of the natural genetic resistance of mice to *Salmonella typhimurium* infection, as a model for typhoid fever. He was able

to show that the *ity* gene controlled early proliferation of salmonellae in the reticulo-endothelial system, that resident macrophages were key to this, and that this was a mechanism distinct from acquired resistance and immunity. A key feature of this work was to recognize the need to follow the growth dynamics of the bacteria *in vivo*, rather than just to rely on death, as a measure of resistance. This lesson has been rather forgotten in recent literature.

I was his first PhD student, and we set out to try to find out more about what T cells and B cells were doing to control *Salmonella* infection after the initial phase of genetic resistance had passed. This was an intense, highly creative and immensely enjoyable time, with the Department of Pathology under the leadership of Peter Wildy being a fantastic place to work. Carlos branched out into vaccinology when he met Gordon Dougan at Wellcome Biotech, where he eventually spent a sabbatical, ostensibly learning molecular biology but in addition invigorating and inspiring the people in the laboratory there to great things. During this time live attenuated *Salmonella* vaccine strains started emerging, especially from the laboratory of Bruce Stocker at Stanford, who became a strong colleague and friend. These provided a new way for Carlos to ask questions about the immune response to salmonellae, but also led to his being able to start developing ideas about delivery of antigens to the immune system via these live attenuated carriers. Carlos made major contributions in this area, not just in understanding how the basic biology and immunology of these systems work, but also in generating vaccines with real potential for exploitation. I am sure that these types of multivalent vaccine will be used, especially in the developing world, but first we will have to overcome Luddite tendencies to reject anything that has been genetically manipulated, and a political and industrial system of vaccine development that is incompatible with the successful development of new vaccines for poor countries.

Carlos continued with these scientific themes throughout his career. He took early retirement from Newcastle after his RAE triumph and I was delighted to be able to offer him space in my laboratory at the Cambridge Veterinary School to continue his research. His latest enthusiasm was to use *Salmonella* vaccine strains to deliver antigens from the worm *Echinococcus* to dogs to try to break the transmission chain that leads to humans with hydatidosis. This is a continuing collaborative effort between Cambridge and scientists in Lyon, Montevideo, Tunisia and Morocco: typical of the type of multinational collaboration that Carlos was so good at generating and fostering. Carlos and Raquel spent about half the year here in Cambridge and the other half in Uruguay where they had built a new and beautiful house near Montevideo. This was idyllic in many ways, and amongst the benefits it allowed stronger links to be developed between scientists in the UK and Uruguay.

Carlos was very generous with his time, and always gave back to his professional colleagues more than he took. He gave service to the SGM and was elected a Fellow of the Academy of Microbiology of the ASM.

Carlos was larger than life. He was the type of man to develop an enthusiasm, go into it until he understood everything about it, then practice it assiduously. Such was his fascination with flying. He owned a microlight plane in England and would always be out flying if the weather was remotely sunny. He was a very careful and thorough pilot, and it is with some incomprehension that I contemplate the fact the he died as a passenger in a microlight being piloted by someone else. An appalling waste of a superb man.

Carlos was a much loved and highly respected man and scientific colleague, and we will all miss him terribly.

Duncan Maskell
University of Cambridge

comment

a microbiologist's view of astrobiology

Is astrobiology really a science? Does it have anything to do with micro-organisms? **Howard Gest** gives his opinion.

A prescient 1964 essay by George G. Simpson discussed the possibility of life beyond the Earth and noted the "*increasing recognition of a new science of extraterrestrial life, sometimes called exobiology – a curious development in view of the fact that this 'science' has yet to demonstrate that its subject matter exists!*" It is now almost a decade since NASA scientists McKay *et al.* dramatically announced the discovery of 'past life' on Mars, evidenced partly by supposed fossils of micro-organisms in a Martian meteorite collected on Earth. The announcement unleashed an unprecedented media frenzy, but within 2 years, careful examination of the meteorite by expert scientists showed that the claims of McKay *et al.* could not be substantiated.

As the Mars microbe story deflated, NASA established a virtual 'Astrobiology Institute', which describes astrobiology as '*study of the origin, evolution, distribution and destiny of life in the universe. Astrobiology represents a synthesis of disciplines – from astronomy to zoology, from ecology to molecular biology, and from geology to genomics*'. This description, which has boundless dimensions, is obviously not the definition of a science.

Words beginning with 'astro' define subjects dealing with stars and celestial bodies. Since there is no biology of any kind known other than that on Earth, 'astrobiology' is an oxymoron. The word is designed to generate public excitement and interest, but conveys the false idea that life has actually been discovered in places other than Earth.

The subtitle of Simpson's remarkable essay is '*We can learn more about life from terrestrial forms than we can from hypothetical extraterrestrial forms*'. Simpson stressed the need for experimental facts, not '*improbability piled on improbability*'. The NASA Astrobiology Institute now awards grants promoting studies on terrestrial micro-organisms that can grow under unusual physical and chemical conditions. The existence of such bacteria is exploited to fuel the tacit hope that there may have been organisms that once lived under the hostile conditions on Mars. Publicity from the Astrobiology Institute strongly implies that terrestrial extremophiles were discovered only recently. In fact, many such bacteria were isolated and characterized by microbiologists long before the Space Age. For example, the discovery, by Benjamin Volcani, of extreme halophiles (e.g. *Halobacterium*) in the Dead Sea in the 1940s. During the 1970s, Thomas Brock and others isolated and described several kinds of extremophiles, including a variety of thermophilic micro-organisms (see his important 1978 book).

References to the older literature on the extraordinary range of environmental conditions under which bacterial species can grow can be found in the classic book *Bacterial Metabolism* by pioneering British microbiologist Marjory Stephenson. The final paragraph of her book, published in 1949, notes '*It is impossible to exaggerate the importance of the variability of the bacterial cell or the desirability of studying the laws regulating it. Biochemically, bacterial cells are the most plastic of living material, even as compared with other micro-organisms. The bacterial cell, by reason of its small size and consequently relatively large surface, cannot develop by maintaining a constant chemical environment, but reacts by adapting its enzyme systems so as to survive and grow in changing conditions. It is immensely tolerant of experimental meddling and offers material for the study of processes of growth, variation and development of enzymes without parallel in any other experimental material.*'

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Further reading

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