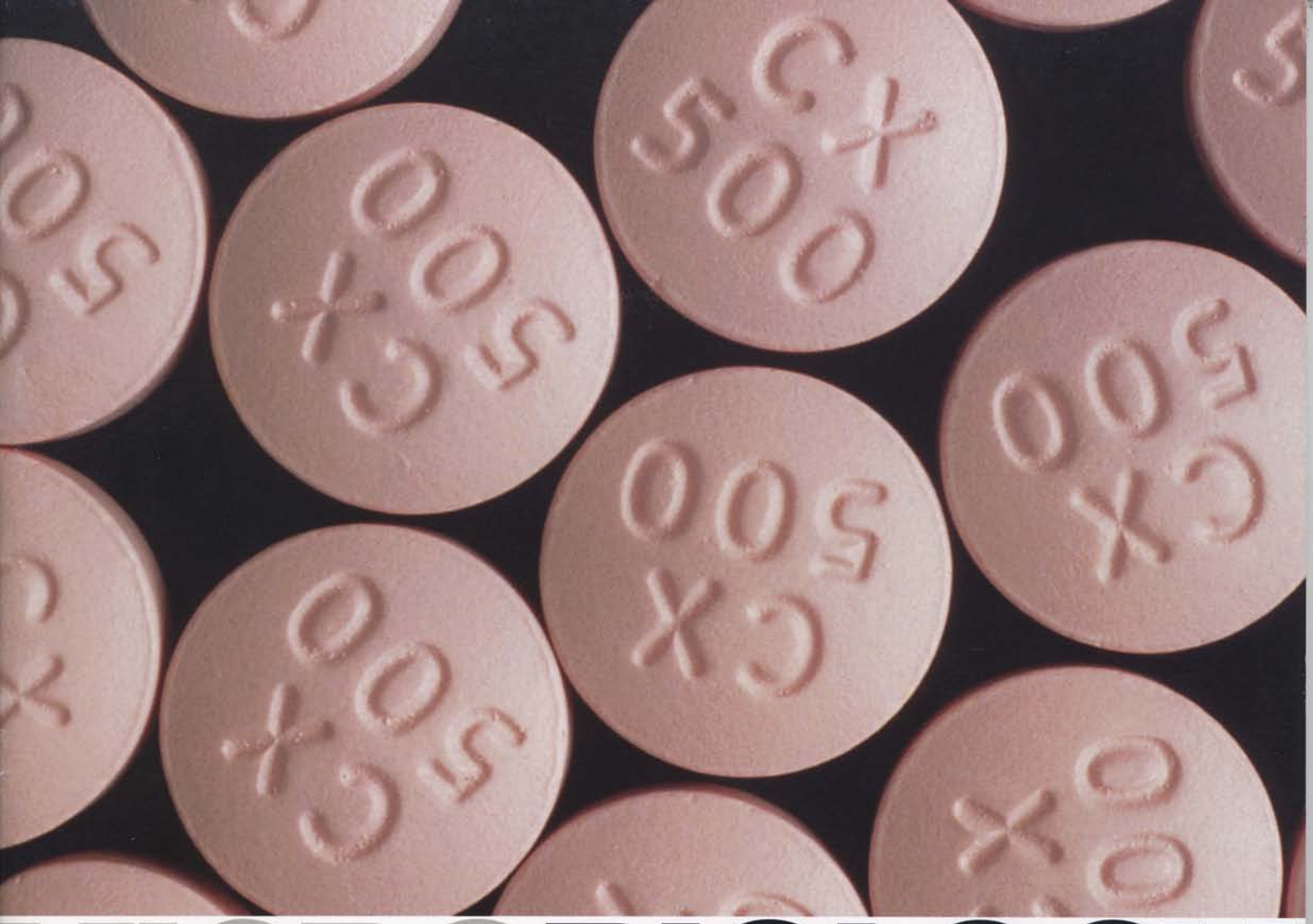

MICROBIOLOGY TODAY

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Contents

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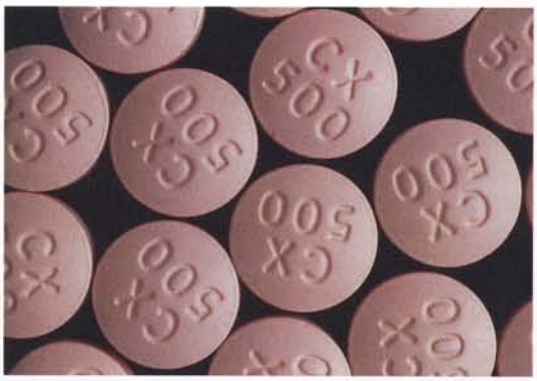


Above: 500 mg tablets of the antibiotic cephalexin. *James King-Holmes / Science Photo Library*

Vol. 31, Part 2, May 2004

Only a few years ago scientists thought they had seen off infectious diseases, but the microbes fought back. In this issue we explore the current state of play with antimicrobials, alongside some other interactions between micro-organisms and drugs.

Most antibacterial therapy still depends on classes of antibiotics developed 20 years ago, but increasing resistance means that new types of drugs are needed. David Payne recounts (pp. 55–57) how different approaches are required, because genomics, although opening up possibilities, cannot provide all the answers.

Despite the problems, there is still hope. Information gleaned from genome sequencing can be used to determine structures of gene products. This 'structural genomics' has many applications in the search for new antimicrobials according to Ian Boucher and colleagues (pp. 74–75). David Hopwood explains how new antibiotics from *Streptomyces* may yet be produced by applying genetic and chemical techniques (pp. 64–65). Research into antivirals is making great progress, as Hugh Field and Erik De Clercq describe (pp. 58–61) whilst Deirdre Devine explores the potential of host defence peptides as anti-infective agents (pp. 70–72).

Beliefs that using biocides to raise standards of hygiene in both the home and industry may have contributed to the development of antimicrobial resistance are challenged by Peter Gilbert and Andrew McBain (pp. 62–63). They think that the benefits far outweigh the risks.

The microbial metabolism of narcotic drugs such as heroin and cocaine is covered by Deborah Rathbone and Neil Bruce (pp. 66–68). These findings are offering some interesting applications.

In Comment, Nick Russell (p. 112) pleads for the unique environment of Antarctica to be protected from bioprospectors who seek to exploit the potential of the resident psychrophiles.

These articles appear in addition to all the regular features and reports of Society activities.

Articles

Regular Features

Other Items

Letters

In the 'Comment' feature of the November 2003 issue of *Microbiology Today*, Colin Howard and Geoffrey Schild asked if SGM provides enough support for veterinary microbiology. Here are some readers' responses. Further correspondence on this issue is welcome. email **mtoday@sgm.ac.uk**

Veterinary microbiology: SGM's role

I note that SGM is currently considering how best it may serve veterinary microbiologists and that you seek views on this to which I would comment as follows:

As someone who has worked with veterinary, food and plant bacteriology, as well as having been trained in medical microbiology, perhaps I am better positioned than most to see the benefits that can accrue from not sticking rigidly within our own isolated areas. There needs to be much more integration between veterinary and medical microbiologists in particular, but also across other disciplines as well. Organizations such as the SGM can play an important role in facilitating this progression.

The veterinary topics featured in the November issue of *Microbiology Today* were a significant milestone and dare I say possibly overdue. A range of subjects was covered although the potential zoonosis element appeared to be key throughout. This perhaps reflects one of the problems with veterinary microbiological research in that there often has to be a zoonotic link to attract funding, but again emphasizes the importance of medical and veterinary microbiologists working together. There can be little doubt that a further similar issue could cover a completely different range of topics, both zoonotic and non-zoonotic and still remain as engrossing. What would be more progressive, however, would be an issue that covers a range of subjects but has both veterinary and medical authors (or from other specialisms where possible) for each topic. Obviously this would reduce the overall number of topics covered, but I think it is worth considering and the format could be copied for different specialisms as well.

I am not sure what the breakdown of veterinary members of the SGM is but could consideration be given to introducing a veterinary group? Such a group was introduced by the ASM only a few years ago, prior to which most veterinary members belonged to the clinical group.

Perhaps a veterinary session could be included at one of the SGM meetings; however, in saying so I appreciate that you require to get an audience and this may again point us back towards zoonosis.

I hope these comments are helpful.

Geoff Foster, SAC Veterinary Services, Inverness

I too share the concerns of Professors Howard and Schild regarding the current state of veterinary microbiology. One of the problems must be the increased time spent on clinical subjects at the expense of pre-clinical subjects. Basic knowledge is also lacking on many of the exotic species in which the modern graduate may wish to specialize. For those wishing to specialize in microbiology the training opportunities and the number of possible jobs tends to be very limited compared with other disciplines, e.g. pathology.

The Royal College of Pathologists SAC in Veterinary Pathology has set up a working group to determine the feasibility of veterinary microbiologists obtaining their membership by examination since the only route at the moment is by presentation of published work. I should be grateful if you could keep me informed of any developments within the Society in this area, and to offer my assistance.

Clifford Wray, BVM&S MRCVS PhD RFColl.Path.

At one time or another, before I retired nearly 15 years ago, I worked on influenza, *Chlamydia psittaci* and *Listeria monocytogenes* and, more recently, was involved in a minor administrative way in research on BSE/vCJD. Accordingly, I have much sympathy with the views expressed by Colin Howard and Geoffrey Schild in their article in *Microbiology Today*.

You will know that Cirencester is home to the Royal Agricultural College and although I am not aware of its current research or other activities in the field of food-borne disease or zoonoses, it may well be that such institutions could be interested in the SGM's well-conceived promotion in these areas.

Roy Postlethwaite, Cirencester

In response to the article on veterinary microbiology, I would like to suggest a field for action. I believe that high-resolution phylogenetic sequence databases for microbes of clinical relevance would be of enormous benefit to the research community and society alike (see http://www.separationsnow.com/basehtml/SepH/1,1353,6-1-1-0-742-news_detail-0-742,00.html). I believe that the strongest impact of such databases on research would be witnessed in veterinary microbiology. I wonder if the SGM would find ways to lobby for such an initiative?

Levente Bodrossy, Austrian Research Centres Seibersdorf, Austria

Readers with interests in veterinary microbiology should note the following sessions at forthcoming SGM meetings:

- Trinity College Dublin
  8 September 2004
  Zoonotic infections
- Heriot-Watt University
  6 April 2004
  Emerging diseases of wildlife and farmed animals

Antimicrobials – where next?

David J. Payne

New drugs are needed to meet the challenges posed by superbugs. David Payne explains why genomics, although it has led to many advances, cannot provide all the answers.

The need for new antibiotics is a well known concern of health care professionals. Not surprisingly anxiety over the issue has percolated to the national press with headlines such as '*Superbugs: Crisis Grows*' (*Daily Mail*, 6 December 2003) and '*Superbug Apocalypse*' (*Daily Mail*, 30 September 2003). Remarkably, current antibacterial therapy remains largely dependent on antibiotic classes discovered more than 20 years ago. Resistance to these antibiotics is increasing (Fig. 1) and, even more worrying, is the emergence of pan-resistant organisms in our hospitals. For many years antibiotic research was focused on making new derivatives of these established classes of antibiotics, but the pre-existing resistance mechanisms are compromising their further development. Consequently, entirely novel classes of antibiotics are needed for the future.

In the mid-1990s bacterial genomics was believed to be the technological advance that would rapidly provide much needed new classes of antibiotics for the 21st century. However, here we are in 2004 and no new class of broad spectrum antibiotic has reached clinical use in the last 20 years; the prospects for novel acting antibiotics being launched in the next 5–10 years are frighteningly low, especially with the alarming withdrawal of many companies from this therapeutic area. Consequently, this review will illustrate how genomics enabled the industrialization of novel antibiotic target selection and validation, give an overview of the processes and scientific complexities of progressing from genome to antibiotic and provide a perspective of where we go from here.

Bacterial genome sequencing

The first bacterial genome was sequenced in 1995 and with technologies capable of sequencing an entire genome in just days, it is not surprising that as many as 100 bacterial genomes are now available. With respect to antibiotic discovery, access to a complete genome for a particular organism reveals all the potential proteins (targets) that could be exploited as antibacterial strategies.

Target selection

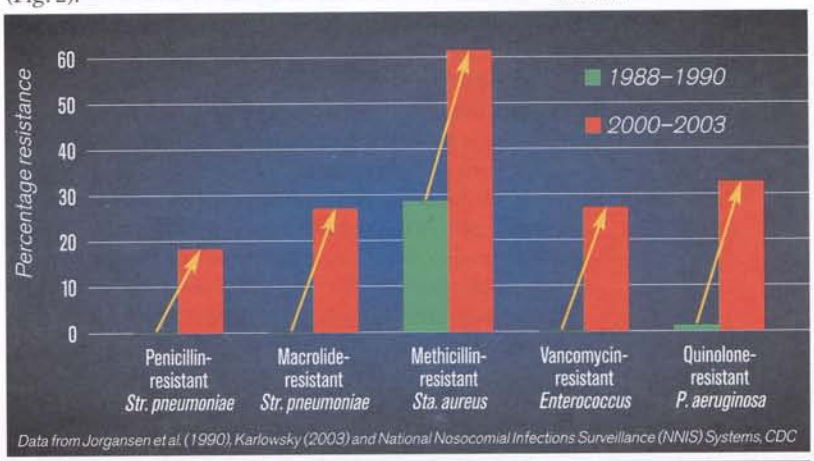
Novel target selection is possible on a scale and accuracy unimaginable in the pre-genomic era. For example, if seeking a Gram-positive-only antibiotic, bioinformatics can identify genes only present in clinically important Gram-positives, but absent from Gram-negatives. Alternatively, if designing an antibiotic to treat a specific set of bacterial infections (e.g. respiratory infections or urinary tract infections) targets can be selected that are present in the common causative bacteria. Access to the human genome also enables evaluation of the potential selectivity of a novel antibacterial target. If a human homologue exists, in-depth comparison with the bacterial version is necessary to assess the likelihood of selective inhibition of the bacterial target. The goal is to identify targets that are present in a clinically relevant spectrum of pathogens with a good selectivity rationale.

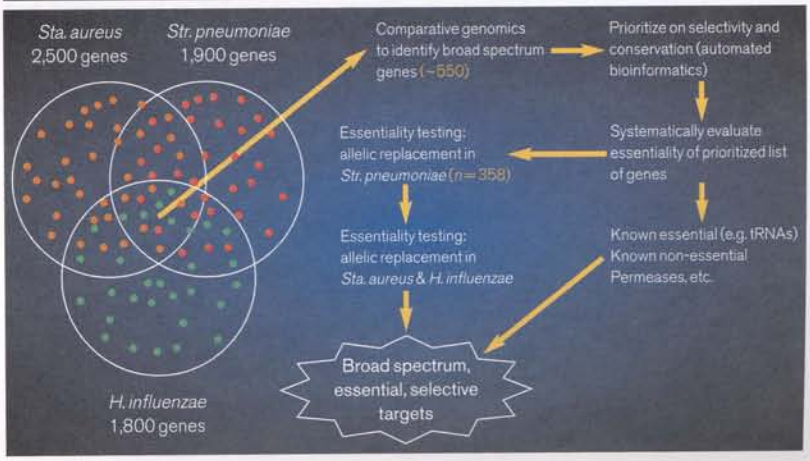
Target validation

After selecting an antibacterial target, the next steps are proving that it is critical for survival and validating that inhibition of its function will result in bacterial death. A variety of methodologies have been developed to assess this. The simplest is to selectively delete the gene of the target from the genome; if the organism is able to sustain growth despite loss of the gene, this demonstrates that the target is not essential. Gene regulation approaches (e.g. inducible promoters and antisense) have also been used successfully, with essential genes being identified by a concomitant decrease in growth following down regulation of the gene. Many of these approaches have been optimized to provide rapid throughput target validation. For example, GlaxoSmithKline (GSK) developed robust systems for evaluating the essentiality of genes in *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus* and more than 350 targets were evaluated. Overall, genomics has enabled the industrialization of novel antibiotic target discovery and validation (Fig. 2).

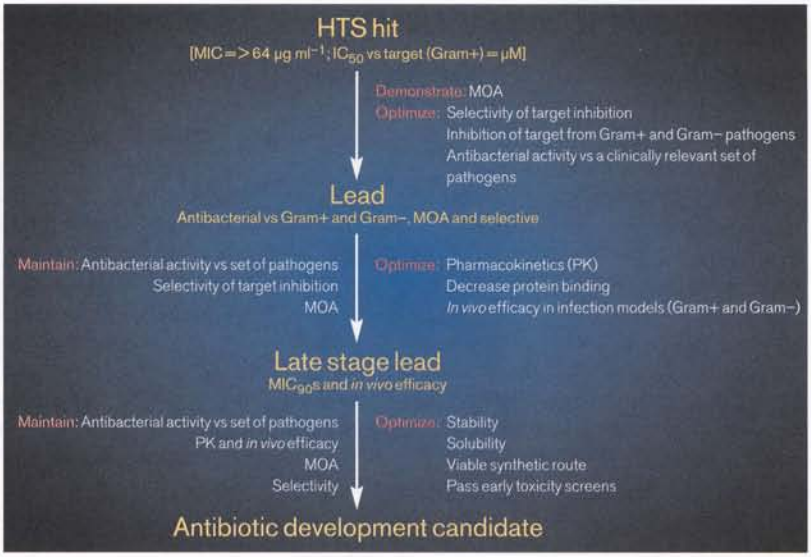
BELOW (TOP):
Fig. 1. Increasing resistance to established classes of antibiotics

BELOW (BOTTOM):
Fig. 2. Industrialization of novel antibiotic target discovery and validation.





RIGHT:
Fig. 3. The complexities of chemical optimization of 'hits' from HTS to antibiotic development candidates.



High throughput screening (HTS)

Following the identification of validated, selective targets the next step is to find an inhibitor of the target by high throughput screening of a diverse set of compounds. Producing sufficient reagents and configuring an assay to be run at high throughput (screening > 100,000 compounds) can normally be achieved fairly efficiently for antibacterial targets, facilitated by the fact that production of the many milligrams of protein needed for HTS can be easily achieved via expression in bacterial hosts.

Having obtained high quality hits from HTS, the application of medicinal chemistry is necessary to introduce all the necessary properties for a successful antibiotic; this process is known as 'lead optimization'.

Hits from HTS

Identification of hits and the lead optimization steps (Fig. 3) are the two most challenging aspects of delivering new antibiotics from genomics. First, the hit rate of HTS of antibacterial targets is less than that achieved for targets from other therapeutic areas. GSK bases this by comparing data from other therapeutic areas with the results of more than 50 screens run on antibacterial targets. There may be a combination of reasons, but analysis of the chemical properties and parameters of known antibacterial compounds suggests that such properties may not be well represented in standard screening collections and a broader or more 'antibacterially relevant' diversity has to be acquired and screened. Consequently, the poorer hit rate from HTS of antibacterial targets compromises success at the earliest step in the cascade.

Lead optimization of hits to antibiotics

It is likely that a hit from HTS will possess selective micromolar inhibitory potency against the target with low-level antibacterial activity. At this early stage it is imperative to demonstrate that the compound's antibacterial effect is clearly a result of inhibition of the target and not due to potentially non-specific effects. Providing robust mechanism of action (MOA) data can be highly complex and requires significant biochemical and complex proteomic and gene expression approaches (e.g. gridding).

Once MOA is confirmed, significant medicinal chemical resources are required to optimize the hit into a molecule that has all the requisite properties for the development of a successful antibiotic. This process has an additional aspect that is very different from other therapeutic areas in that ideally the final molecule needs to possess antibacterial activity against more than one pathogen, and optimistically, multiple pathogens. Essentially, this means optimizing the inhibitory activity against the target from each of a key spectrum of pathogens. Although the target is deliberately selected to be highly conserved across these pathogens, the architecture of the active sites will differ slightly, which can add to the challenge of finding one molecule that fits all. Furthermore, even if a molecule has been identified that has equal inhibitory potency against the targets from all the key organisms, considerable challenges still exist in optimizing penetration through the bacterial wall and membranes which are characteristically different in each species. Consequently, it can take a considerable effort to identify molecules that demonstrate good target inhibitory activity and thus antibacterial activity across multiple pathogens.

Then, whilst maintaining the broad antibacterial and target inhibitory activity, other important attributes are necessary. These include favourable pharmacokinetics (PK), efficacy in animal models, lack of toxicity and even parameters such as appropriate solubility, stability and a commercially viable synthetic process (Fig. 3). One other challenging factor is that we are often dealing with an entirely new chemical entity that has never been previously evaluated for pharmacological activity and so no structure activity relationship (SAR) exists. This is in contrast to delivering new derivatives of established classes of antibiotics such as cephalosporins, macrolides or quinolones where decades of SAR exist to facilitate the lead optimization process. Finally, once a molecule

has been identified with all the requisite preclinical properties, it enters the development phase. Here, good, predictable animal infection models and relatively rapid clinical trials with clearly defined end points facilitate a higher probability of success than in some other therapeutic areas.

But there are surprises...

Progressing a project to identify an antibiotic with an entirely novel mechanism of action can be an adventure into the unknown compared with finding new derivatives of established classes of antibiotics. This is exemplified by the methionyl tRNA synthetase (MRS) target. This target is essential in a broad spectrum of bacterial pathogens, and as part of a strategic effort to screen all 19 of the Gram-positive tRNA synthetases we identified a promising inhibitor of MRS. Chemical optimization of this hit successfully yielded highly potent antibacterial compounds which cured multi-resistant bacterial infections in animal models. However, it was found that the MRS (MRS1) screened in the HTS only existed in around 50 % of clinical isolates of *Str. pneumoniae*; the other 50 % possessed a different MRS, MRS2. Despite overall high similarity between MRS1 and MRS2, this chemical series achieved potent inhibition of MRS1, but inhibition of MRS2 was severely compromised because of a leucine to tryptophan difference in the active site of MRS2. Consequently, the series possessed unacceptably poor antibacterial activity against 50 % of all *Str. pneumoniae* clinical isolates. Extensive efforts to modify the molecule to achieve inhibition of both MRS types whilst maintaining its other drug-like qualities failed. This experience illustrates the need for target validation beyond the genome, emphasizing that the genomes we have access to only represent the genetic make up of a single organism which may not be entirely representative of its species.

Where next ?

It is easy to accuse genomics of not delivering! However, this is really not true as genomics could only ever identify novel antibacterial targets and new genomic technologies. Due to genomics, we now probably know all the potential ways to kill bacteria and experiments previously conducted on a gene scale can now be performed to give readouts on the entire genome. Making antibiotics from genomics depends heavily on high throughput screening and successful optimization of hits from these screens. The preclinical complexities and hurdles of these factors were underestimated in the genomic era and are the two main issues that have compromised the delivery of antibiotic development candidates and thus new drugs.

So where do we go from here? Antibiotic research now needs to focus on thoroughly validated targets and provide the substantial medicinal chemical resource necessary to develop promising antibiotic leads that act on these targets. As part of this strategy, a return to microbiology is required to provide high quality and fast *in vivo* and *in vitro* microbiological evaluation of promising preclinical antibacterial compounds. Success at high throughput screening also needs to be addressed. Acquisition and generation of novel compound libraries especially suited to the chemical parameters common to antibacterial compounds – 'antibacterial targeted chemical diversity' – is one welcome approach. In addition, screening new generations of natural product diversity, such as gene shuffling of known secondary metabolite pathways, could also yield new compounds to screen against antibacterial targets.

In conclusion, since 1995 big pharma and the biotech industry have applied immense resources to exploiting genomics in an attempt to identify new antibiotic molecules. Although this has provided an unprecedented number of antibacterial strategies, success measured in terms of new antibiotics has been disappointingly poor. This, along with changing corporate priorities and regulatory issues, has contributed significantly to many companies withdrawing from antibiotic research, despite the fact that the medical need for novel acting antibiotics remains unquestionable. At GSK we hope to increase prospects for delivering new antibiotics by applying significant microbiological and medicinal chemistry resources to tackle directly the preclinical challenges and use the very considerable knowledge from bacterial genomics to facilitate the success of our antibacterial research.

Dr David J Payne is Director of Microbiology in the Microbial, Musculoskeletal and Proliferative Diseases CEDD at GlaxoSmithKline, South Collegeville Rd, Collegeville, PA19426, USA.
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Further reading

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Antiviral drugs – a short history of their discovery and development

Hugh J. Field and Erik De Clercq

For many years it was believed that there were no effective antiviral drugs. Since the late 1950s scientists have made great progress in this area as Hugh Field and Erik De Clercq describe.

The concept of specific antiviral therapy and a false dawn

The 1946 edition of van Rooyen and Rhodes' *Virus Diseases of Man* introduced the concept of specific therapy for a number of virus infections, including mumps and smallpox. This early work focused on the use of the current bacterial antibiotics, including sulphonamides. The futility of these early attempts led to the dogma that viruses are not susceptible to 'antibiotics' and for two decades virologists were taught that selective toxicity for these obligate intracellular parasites was unattainable. Several lines of research were to overturn this *idée fixe*. In 1957 came the famous first description by Isaacs and Lindenmann of interferon. Human interferons were subsequently developed for the treatment of particular virus infections, i.e. hepatitis B and, more recently, hepatitis C virus infections, as pegylated interferon, combined with ribavirin. However, the discovery of the interferons in the late 1950s was something of a false dawn.

Idoxuridine: the first useful antiviral nucleoside analogue

Many in the antiviral field recognize as a most important early milestone the description of 5-iodo-2′-deoxyuridine (idoxuridine, IDU) by Dr Bill Prusoff in 1959 and the realization of its antiviral properties. The first publications on this and similar nucleoside analogues appeared in cancer journals and it is clear that the aim was to develop molecules to interfere with DNA synthesis in order to produce cytostatic or cytotoxic drugs for the treatment of neoplastic disease. However, an important by-product of this work was the discovery that IDU was a specific inhibitor of certain large DNA viruses, most notably herpes simplex virus (HSV). The compound is cytotoxic and was therefore only suitable for topical application, for which it remains in use to the present day. The development of IDU from laboratory inhibitor to useful antiviral drug was driven by several notable pioneers, especially the ophthalmologist Dr Herbert Kaufman who proved its clinical value in 1962 and, subsequently, that of trifluorothymidine (TFT) in 1964.

The first description of the antiviral activity of adenine arabinoside (vidarabine, ara-A) by M. Privat de Garilhe and J. De Rudder also dates from the avant-garde year 1964. Ara-A was the first of the nucleoside analogues to be sufficiently non-toxic to be given systemically and the work of Dr Richard Whitley proved beyond doubt the clinical value of this compound, showing for the first time that, providing treatment was commenced early in the disease, it was possible to curtail herpes zoster in the immunosuppressed and reverse the potentially lethal progression of herpes encephalitis and the overwhelming herpes infections that occasionally occur in the newborn.

Selected milestones in antiviral drug development

1951	β-Thiosemicarbazone	Hamre *et al.*
1957	Interferon	Isaacs & Lindenmann
1959	IDU	Prusoff
1961	Hydroxybenzylbenzimidazole	Tamm & Eggers
1961	Guanidine	Barrera-Oro & Melnick
1962	IDU (clinical effectiveness)	Kaufman
1963	Marboran (clinical effectiveness)	Bauer *et al.*
1964	TFT (clinical effectiveness)	Kaufman
1964	Amantadine	Davies, Hoffmann *et al.*
1964	Ara-A	Privat de Garilhe & De Rudder
1972	Ribavirin	Sidwell, Robins *et al.*
1976	Ara-A (clinical effectiveness)	Whitley
1977	Acyclovir	Elion, Schaeffer, Collins & Bauer
1978	DHPA	De Clercq & Holy
1979	Phosphonoformic acid (PFA)	Helgstrand & Öberg
1979	BVDU	De Clercq *et al.*
1982	Ganciclovir	Verheyden & J.C. Martin
1985	Azidothymidine (AZT)	Mitsuya, Broder *et al.*
1986	ddI, ddC, . . .	Mitsuya & Broder
1986	Adefovir (PMEA)	De Clercq, Holy *et al.*
1987	Cidofovir (HPMPC)	De Clercq, Holy *et al.*
1989	Famciclovir (oral prodrug strategy)	Harnden, Vere Hodge *et al.*
1989 1990	HEPT/TIBO	De Clercq, Baba, Pauwels & Janssen
1990	Saquinavir	J.A. Martin, Roberts *et al.*
1991	3TC	Belleau *et al.*
1993	Tenofovir (PMPA)	Balzarini, De Clercq & Holy
1993	Relenza	von Itzstein *et al.*
1997	Oseltamivir	Kim *et al.*

Poliomyelitis, smallpox: important early antiviral targets

We will return to herpes antivirals, but first we should remember the origins of several other lines of antiviral research and the early pioneers. Poliomyelitis was still a serious threat in the developed world when guanidine and 2-(α-hydroxybenzyl)benzimidazole (HBB) were shown to be specific inhibitors of this small, positive-strand picornavirus and other picornaviruses (i.e. Coxsackie and Echo) as early as 1961 by J.G. Barrera-Oro and Joe Melnick, and Igor Tamm and Hans Eggers, respectively. The latter promoted the concept of specific antiviral therapy for polio and their lectures and writing much influenced the field in the 1960s, although, in the event, polio was eventually controlled by vaccination rather than chemotherapy. Another important virus

ABOVE:
Picture taken at the 10th International Conference on Antiviral Research, Atlanta, 6–11 April 1997. Many of those in this photograph have made a major contribution to the development of antivirals.
1, G.L. Galasso; 2, Mrs Galasso; 3, W.H. Prusoff; 4, E.R. Kern; 5, R.F. Schinazi; 6, J.C. Martin; 7, G.B. Elion; 8, R.J. Whitley; 9, H.J. Field; 10, J.-L. Imbach; 11, Mrs Shigeta; 12, S. Shigeta; 13, D.C. Liotta; 14, J.A. Secrist III; 15, J.-C. Graciet; 16, L.J. Stuyver; 17, D. Parker; 18, C.R. Cusick; 19, K. Shockley; 20, B. Öberg; 21, K.Y. Hostetler; 22, A. Kwong; 23, C. McGuigan; 24, R.W. Sidwell; 25, K.K. Biron; 26, J.W. Mellors; 27, E. De Clercq; 28, P.D. Griffiths; 29, L.M. Mofenson; 30, J.-P. Sommadossi; 31, A. Molla; 32, D. Schaeffer; 33, C. Laughlin; 34, N. Bischofberger.
COURTESY DR RAYMOND F. SCHINAZI, EMORY UNIVERSITY, GA, USA

threat was that of smallpox caused by variola virus, which is among the largest of all viruses with a double-stranded DNA genome comprising more than 200 genes. The compound β-thiosemicarbazone was first reported to be an inhibitor of a related poxvirus, vaccinia virus, in 1951 by D. Hamre, K.A. Brownlee and R. Donovick. Dr John Bauer at the then Wellcome Foundation Laboratories in Beckenham, UK, led the team which developed the drug marboran, a β-thiosemicarbazone derivative. Marboran was shown in several trials to have some clinical efficacy both for the treatment of smallpox and the complications of vaccinia following vaccination. Furthermore, it was shown that marboran was a highly effective agent for chemoprophylaxis in the management of smallpox contacts. Smallpox was shortly to be eradicated by means of the WHO vaccination scheme and work on marboran ceased. However, recently there has been renewed interest in antipoxvirus agents as a result of the threat of smallpox being reintroduced by an act of terrorism.

Treatments for influenza virus infections

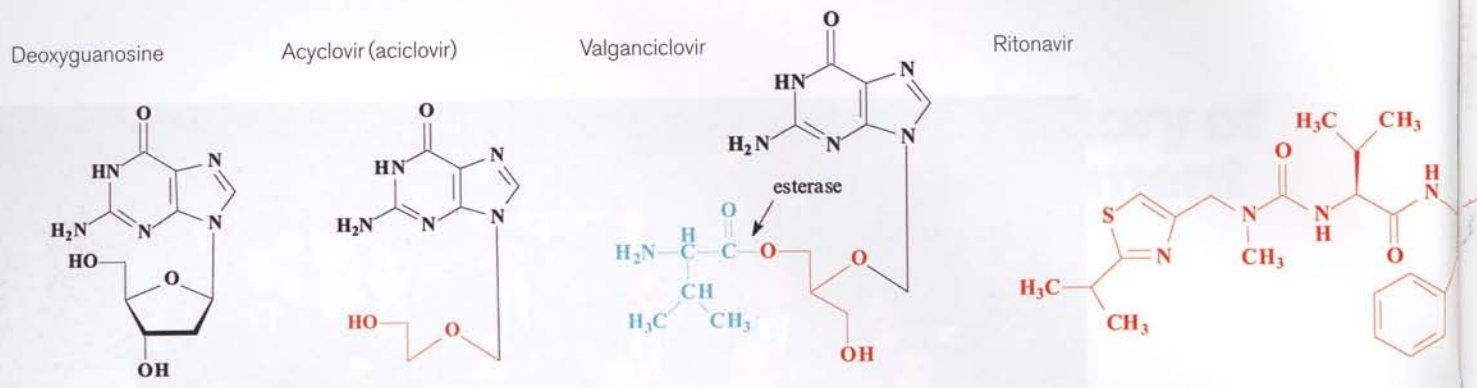
Influenza was also an early antiviral target, and in 1964 it was reported by C.E. Hoffmann and co-workers that amantadine was a specific inhibitor of the negative RNA strand virus, influenza A. Amantadine and its sister compound, rimantadine, were later shown to act by interaction with the viral M2 protein which forms an ion channel during the early stages of virus replication. As for almost all other specific antiviral agents, resistant mutants were obtained by passage of virus at sub-inhibitory concentrations of the inhibitor and in this case these mutations mapped to the M2 and haemagglutinin (HA) genes. Furthermore, when the compounds were used clinically, resistance developed quickly in patients and this was one of the factors which argued against their widespread clinical use. Rimantadine was, however, widely used clinically in Eastern Europe during the cold-war years, although the data relating to its use in man were not so easily forthcoming. However, the work on amantadine and rimantadine provided a platform for the development of the next generation of anti-influenza drugs that resulted from a programme of rational drug design. The crystal structures of the influenza envelope proteins – HA and neuraminidase (NA) – were solved. Influenza NA was known to interact with sialic acid residues on host-cell plasma membranes and the first of several sialic acid analogues, Neu5Ac2en, designed by M. von Itzstein and his colleagues in 1993, based on the crystal structure of influenza NA, led to the development of 4-guanidino-Neu5Ac2en (relenza), the first NA inhibitor, to be marketed by Glaxo. A difficulty with this compound is its poor oral bioavailability, necessitating its application by means of inhalation. Other NA inhibitors tailored on the sialic acid residue followed, including the successful oseltamivir (developed at Gilead sciences and first reported by C.U. Kim *et al.* in 1997) in which a cyclohexene ring was introduced and a polar glycerol replaced with a more lipophilic side-chain. Furthermore, oseltamivir is an ethyl ester that is orally bioavailable and readily converted to the active carboxylate by esterases in the liver, a prodrug approach first used for the antiherpetic compound famciclovir (see below).

The first broad-spectrum antiviral after interferon

Ribavirin was reported in 1972 by Robert Sidwell, R.K. Robins and their colleagues as a broad-spectrum antiviral acting against many different virus families, notably the negative RNA strand virus, respiratory syncytial virus. It was noted that virus resistance to ribavirin was not detected for any of the susceptible virus families. This may be related to the fact that ribavirin primarily targets a host-cell protein, and, indeed ribavirin (5′-monophosphate) has been found to inhibit IMP dehydrogenase, the enzyme responsible for the conversion of IMP to XMP. Another discovery in the 1970s was the antiherpesvirus activity of the pyrophosphate analogue phosphonoformic acid (phosphonoformate PFA) following the earlier discovery of the lead compound, phosphonoacetic acid (PAA). PFA, described by B. Öberg and developed at the Swedish pharmaceutical company, Astra, suffers from toxicity problems, including nephrotoxicity. However, PFA continues to have a role in managing HSV infections in immunocompromised patients who are resistant to the classical antiherpetic compounds (e.g. acyclovir).

The advent of acyclovir

No history of the origins of antivirals would be complete without acknowledging the enormous impact of the compound acyclovir. Like IDU, acyclovir was the result of a drug development programme not primarily aimed at antivirals. The names of Dr Gertrude (Trudy) Elion



ABOVE:
The chemical structure of a selection of antiviral compounds. Red is used to indicate those parts of antiviral compounds which differ from the natural structure from which they are derived. Blue is used to depict the components of prodrugs that are removed by enzymic action *in vivo* to yield active compounds.
A more complete set of structures accompanies the online version of this article at www.sgm.ac.uk

and Dr Howard Schaeffer (Burroughs Wellcome, USA) are inextricably linked to this compound, although its potent antiviral properties were first uncovered by Drs Peter Collins and John Bauer at the Wellcome Laboratories (UK) where the compound had been sent for antiviral activity evaluation. Dr Bauer coined the term acycloguanosine, although this was subsequently dropped in favour of the generic term acyclovir (aciclovir). Dr Elion and her colleagues produced a definitive mechanism of action and the thoroughness of this work and the associated pharmacological data were crucial to the early acceptance of the compound. Acyclovir was shown to be a substrate for the HSV-encoded deoxyribopyrimidine kinase, usually called thymidine kinase (TK). Acyclovir monophosphate is then further phosphorylated by cellular kinases and the resulting acyclovir triphosphate is a potent suicide inhibitor of the herpes-specified DNA polymerase. The fact that a (deoxy)-guanosine analogue serves as a substrate for the virus deoxyribopyrimidine kinase was a major stumbling block in elucidating the mechanism of action, but eventually this was resolved. Acyclovir has become recognized as one of the safest drugs of all times with almost no adverse affects described during $2^1/_2$ decades of use (apart from those related to low aqueous solubility of the compound), including individuals who have used the compound for 20 years to suppress recurrent HSV. Acyclovir was the very first highly selective antiviral compound, and it was the prototype described as a 'second generation' nucleoside analogue. It eventually became available as an over-the-counter drug in the UK, an unthinkable development even a few years previously.

The prodrug strategy for enhancing oral bioavailability

The fact has remained that its low oral bioavailability gives acyclovir a pharmacological disadvantage. Several new analogues had been discovered to have similar antiviral properties in particular bromovinyldeoxyuridine (BVDU), synthesized by Phil Barr in the Laboratory of Stan Jones and Dick Walker at the Chemistry Department at the University of Birmingham (UK) and shown to be a potent inhibitor of HSV (type 1) and the related varicella-zoster virus (VZV) by Erik De Clercq at the Rega Institute of Medical Research (Belgium). BVDU is now on the market in Germany and other European countries for the treatment of herpes zoster (shingles). Acyclic guanosine analogues other than acyclovir were synthesized in several laboratories worldwide, one of those being ganciclovir (discovered by Julian Verheyden and John C. Martin then at Syntex) that later on would find a niche in the treatment of cytomegalovirus (CMV) infections in immunosuppressed patients.

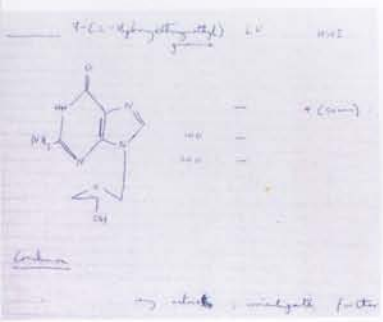
Another acyclic guanosine analogue, penciclovir, was developed in the laboratories of the former Beecham Pharmaceuticals company. Against HSV, penciclovir is comparable in activity and specificity with acyclovir. The realization that penciclovir has even poorer oral bioavailability than acyclovir resulted in a programme of medicinal chemistry led by Dr Mike Harnden which culminated in the synthesis of the molecule that was to become famciclovir. The key point here is this was the first antiviral orally available 'prodrug' (to be later marketed) and brought about a strategy that has been widely repeated for many other antiviral compounds. Famciclovir is rapidly absorbed when given orally and then converted to the active antiviral compound, penciclovir *in vivo*, following host enzymic conversion by two esterase steps and an oxidation step. In parallel work, Burroughs Wellcome developed several potential prodrugs of acyclovir and one of these was the valine ester of acyclovir which came to be known as 'valaciclovir' which is currently in widespread clinical use (for the same clinical indications as acyclovir). In fact, the first prodrugs to be described (back in 1983 by Hubert Vanderhaeghe and his colleagues at the Rega Institute) were the amino acid (glycine, alanine) esters of acyclovir, designed to make acyclovir more soluble in water. The prodrug strategy has now been widely adopted and the neuraminidase inhibitor produced by Gilead, oseltamivir, is one recent example (see above); valganciclovir, the valine ester of ganciclovir being another one.

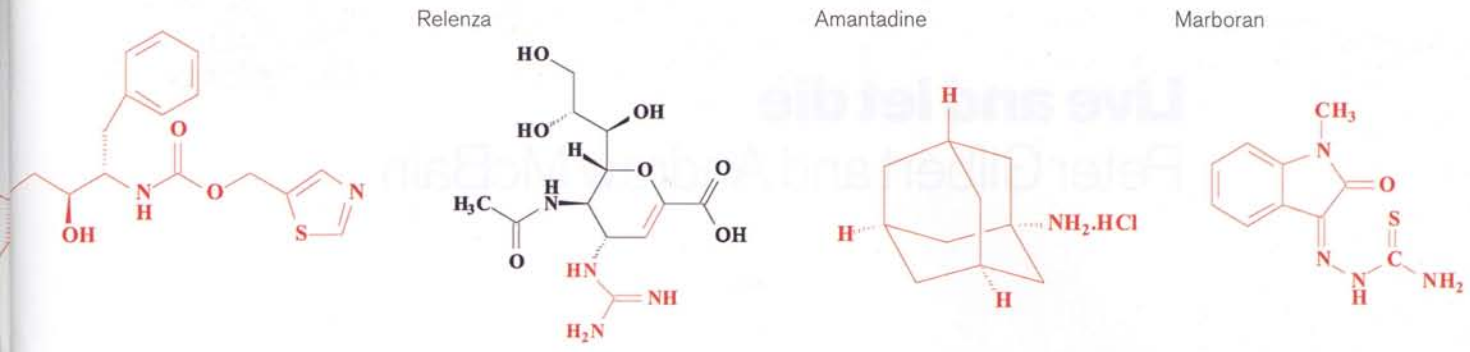
HIV – a new virus threat

The science of antiviral research was well advanced when HIV/AIDS appeared as a major new virus disease in the early 1980s. The first effective antiviral compound (AZT, azidothymidine) was already among the library of compounds screened by Burroughs Wellcome and the National Cancer Institute (USA), and was promptly reported in 1985 to be a specific inhibitor of retroviruses, including HIV. The mechanism of action of AZT is based upon phosphorylation of the drug by cellular enzymes to AZT triphosphate, which then interacts at the substrate-binding site of the HIV reverse transcriptase, thereby acting as a chain terminator. The discovery of AZT was followed by several other dideoxynucleoside (ddN) analogues (ddI, ddC, d4T, 3TC, ABC, (–)FTC) so that at the time of writing seven ddN analogues, also referred to as NRTIs (i.e. nucleoside reverse transcriptase inhibitors) are formally licensed for the treatment of HIV infections. All these NRTIs act in a similar fashion: after their phosphorylation to the triphosphate, they interact as 'chain terminators' of the HIV reverse transcriptase, thus preventing the formation of the proviral DNA that otherwise would eternalize the infectious state (following integration of the proviral DNA into the host-cell genome).

In 1990 it came as a surprise that the HIV reverse transcriptase revealed a second target for interaction of HIV RT inhibitors, namely at an allosteric site, distinct

BELOW:
A page out of Nick Oliver's notebook showing the chemical structure and first description in 1974 of the antiviral activity of acycloguanosine. The conclusion is 'very active; investigate further'.





from where the NRTIs interact. This site was originally dubbed the TIBO-binding site, as TIBO, together with HEPT analogues, were the first compounds found (by E. De Clercq and his colleagues) to interact in this way. Later, a succession of structurally different compounds, now termed NNRTIs (non-nucleoside reverse transcriptase inhibitors) were shown to interact in a manner similar to that of TIBO and HEPT, and of these NNRTIs, three, namely nevirapine, delavirdine and efavirenz, have been currently licensed for clinical use in the treatment of HIV infections.

The elucidation of the HIV genome revealed at an early stage the existence of the virus-specified protease and this was the declared target for several of the leading pharmaceutical companies. The team of chemists and molecular virologists at Roche led by Drs Joe Martin and Noel Roberts achieved the synthesis of saquinavir, the first peptide-based transition state mimetic. Saquinavir was shown to be active at nanomolar concentrations and was among the most potent antiviral substances yet described. Saquinavir was soon joined by several other similar compounds produced by competing companies. At present, seven protease inhibitors have been licensed for the treatment of HIV infections: saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir and atazanavir.

2003 witnessed the advent of the first 'HIV fusion' inhibitor, enfuvirtide (previously called 'T20'), which blocks viral entry by targeting the viral glycoprotein gp41 which is responsible for the fusion of the viral and cellular membranes. A problem with this compound is that, unlike all other anti-HIV drugs, which can be administered orally, enfuvirtide has to be given subcutaneously by injection twice daily.

It should be mentioned that virus drug resistance has not been a problem with herpesvirus chemotherapy (except in immunocompromised patients). However, resistance to antiviral drugs has emerged as one of the most important barriers to efficacy in the treatment of chronic infections, including HIV. In this case the key was to be found in history – the treatment of tuberculosis where cocktails of drugs were found to be necessary for the successful eradication of the mycobacteria over several months. There has been considerable opposition to the possibilities of drug combinations in the antiviral field (probably born from their inherent reputation for toxicity); therefore, the introduction and subsequent recognition of the value of drug combinations for the treatment of HIV infections were not instantaneous, but are now taken for granted.

The acyclic nucleoside phosphonates

The discovery in 1986 of HPMPA or (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine, by Antonin Holy and Erik De Clercq, heralded a totally new concept in the antiviral therapy era, that of the acyclic nucleoside phosphonates. These nucleotide analogues can be viewed as a kind of hybrid between acyclic nucleoside analogues (a class of molecules to which acyclovir, ganciclovir and penciclovir belong) and pyrophosphate analogues (phosphonoacetic acid and phosphonoformic acid), thus combining the assets of both approaches. In this sense HPMPA could be considered a hybrid of PAA (phosphonoacetic acid) with DHPA (2,3-dihydroxypropyladenine), a molecule discovered in 1978 by De Clercq and Holy as a broad-spectrum antiviral agent, but at that time overshadowed by acyclovir. As the first 'nucleotide' analogue, to be endowed with antiviral properties, HPMPA would subsequently give rise to numerous derivatives, three of which would eventually gain formal acceptance for the treatment of a wide variety of virus infections: cidofovir for the treatment of herpesvirus infections (CMV in AIDS patients), adefovir for the treatment of chronic hepatitis B and tenofovir for the treatment of HIV (AIDS), the latter two in the form of their oral prodrugs, adefovir dipivoxil and tenofovir disoproxil, respectively. Cidofovir, in addition to the indication for which it has been licensed (CMV retinitis in AIDS patients), also offers great potential for the treatment of papilloma-, adeno-, herpes- (other than CMV) and poxvirus infections (i.e. vaccinia, variola, monkeypox, molluscum contagiosum, orf). This is gratifying knowledge, as cidofovir may be useful in the prophylaxis and/or therapy of variola virus infections (smallpox) and complications (such as disseminated or progressive vaccinia) following vaccination with the smallpox vaccine vaccinia in immunocompromised patients.

Conclusions

Many decades after the birth of antibiotics, antivirals have, at last, definitely come of age – 37 antiviral drugs have been formally approved for the treatment of viral diseases. Their applications are primarily aimed at therapy of herpesvirus (HSV, VZV, CMV) as well as HIV, HBV, HCV and influenzavirus infections. Concomitantly with the availability of so many antiviral compounds, the genome sequences of many viruses have become available, and the structure and functions of many virus proteins known, thus defining novel specific targets for rational drug design. The difficulty of translating specific inhibitors into effective drugs remains a major task for the medicinal chemist and 'serendipity', which has aided virologists on several notable occasions in the past, will likely still have a role to play in the future.

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Live and let die

Peter Gilbert and Andrew McBain

The risks of anti-bacterial resistance developing from the use of biocides may well have been over-stated. Peter Gilbert and Andrew McBain argue that health and hygiene are being compromised as a result.

In the late 19th and early 20th centuries major advances were made that led to significant improvements in public health, life expectancy and quality of life. These improvements came through recognition of the role that particular micro-organisms play in the transmission and spread of human disease, and through the implementation of routine strategies for their avoidance. Central to these strategies was the introduction, and routine deployment of, chemical disinfectants and antiseptics. These included many formulations based on natural products such as pine-oil and coal tar, together with the early by-products of the burgeoning chemicals industry – phenolics, cationic surfactants, alcohols and dyestuffs.

Many of these agents, or their derivatives, first used over 100 years ago, remain prominent today. Studies of their bactericidal mechanisms of action were numerous and fruitful in the 1950s and 60s, but waned somewhat in the 1970s as the interests of the pharmaceutical giants moved towards antibacterial agents with therapeutic potential. Such early studies indicated a wide range of targets for virtually all of these molecules that, together with degrees of mammalian cell toxicity, limited their uses to surface disinfection, preservation, and in man, topical applications. Many of the agents were surface-active and relatively lipid-soluble, and as a result had actions upon cells that grouped them as 'biological detergents with membrane-active activities'. Generally the molecules were biodegradable and did not accumulate within the environment.

Over the last century periodic studies have reported on the antimicrobial effectiveness of such molecules towards diverse collections of human and environmental isolates. There appears to have been no functionally significant change in the susceptibility of the target bacteria over this period of extended use. Our experience of the use of antibiotics in therapeutic applications has been in direct contrast to this, with the development and spread of antibiotic resistance increasing since the early 1960s.

In the clinic, antibiotic resistance is currently viewed as a major threat. Common nosocomial pathogens that express resistance towards multiple antibiotics are being increasingly detected both in hospitals and in general practice. It is generally accepted that the main cause of this problem has been, and still is, widespread inappropriate use and over-prescribing of antibiotics in clinical medicine, animal husbandry and veterinary practice. Concerns about bacterial resistance have led to calls for increased education, of both public and professionals, in the correct use of antibiotics.

Since as many as one-third of hospital-acquired infections are believed to be preventable, then more stringent infection control measures have also been advocated to reduce the transmission of what are now often intractable infections. These measures recognize the tremendous contributions that antisepsis has made over the last century towards our current advanced state of public health. Indeed, if reductions in the number of infections requiring antibiotic treatment can be achieved through effective hygiene, including the use of antiseptic products such as medicated dressings and sutures, then this will delay increases in the incidence of antibiotic resistance. Accordingly, it is important to ensure that the use of antiseptic products is not discouraged in situations where it is part of good hygienic practice and where there may be tangible reductions in the transmission of infection.

New biocide products

It is against this background that the last decade has seen a spectacular increase in the number of consumer products that contain added biocide or make claims of antibacterial potency. Such products not only widen the range of formulations intended to disinfect and sanitize surfaces, but have also introduced the concept of antibacterial activity to a wide range of plastics (wraps, food storage containers, white goods, flooring) and textiles (socks, shirts, sportswear, carpets). In this latter instance the outcomes of the implied hygiene are unclear and often dubious. One of the commonly deployed biocides is Triclosan, a broad-spectrum bisphenol that has been in use for over 35 years as an adjunct to hygiene in oral and other personal care products, as well as providing a topical treatment for staphylococcal skin lesions. The general opinion was that Triclosan acted in a multifaceted manner akin to other membrane-active phenolics. This illusion was apparently shattered when in 1998 it was shown that Triclosan selects for mutants in the *E. coli fabI* gene. *fabI* encodes enoyl-acyl carrier protein reductase, an essential enzyme involved in the synthesis of fatty acids, for which Triclosan was identified as a potent inhibitor. Somewhat worryingly, Triclosan shares this target with some current therapeutic agents, including the antitubercular drug Isoniazid. Whilst the clinical importance of Triclosan lies primarily in its efficacy against Gram-positive skin infections and the reports of laboratory-acquired Triclosan resistance were restricted to Gram-negative bacteria, there is considerable homology between the enoyl reductases of *E. coli* and *Staphylococcus aureus*. The two enzymes are functionally interchangeable, and mutations in the *S. aureus fabI* are capable of conferring Triclosan resistance.

Misconceptions and the media

The scene was set, the actors cast and the curtain was about to rise. The studies with Triclosan suggested that the actions of biocides were not necessarily directed at multiple targets and that in some cases they might act at one or two specific cellular targets in much the same way as antibiotics. Were these targets to be shared with an antibiotic, for which such interactions are

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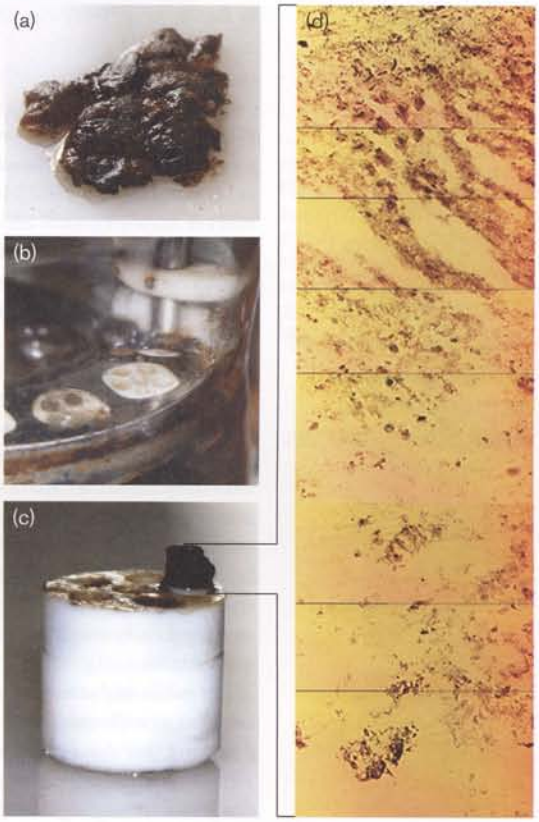
critical, then it was possible that the use of biocides might influence the selection and propagation of resistance. These possibilities were made even more pressing by a concurrent expansion of products deploying biocides and antibacterial claims being made to consumers. In the absence of further information it was not long before the tabloid press were informing us of the dangers proffered by the indiscriminate use of antibacterial products, and calling for their abolition.

Sadly, in spite of the economic importance of many of the active ingredients, knowledge of their mechanisms of action had not been advanced since the dark ages of the 1960s and 70s and for many classes of agent these assertions could not be refuted. Even for those biocides for which multiplicity of target had been clearly demonstrated, susceptibility towards each target was variable and dependent on the concentration of the biocide. It was conceivable that mutations in single intracellular targets could confer selective advantage to bacteria that were exposed to sub-lethal concentrations (i.e. remote from the site of use). Thus, whilst it was unlikely that use levels of biocide could select for resistance at their point of use, residuals, accumulated in the environment, might. Furthermore, it had been shown that at sub-lethal concentrations many of the active molecules had the capacity to select for hyper-, or even constitutive-expression of multidrug-efflux pumps in a range of organisms. Such mutants, whilst unaffected in their response to use-concentrations of biocides, possess a reduced susceptibility towards a range of antibiotics that is sufficient to lessen their therapeutic effectiveness.

Testing tells

Good news does not sell newspapers, so in the last 5 years, whilst the alarm has been maintained, little other relevant research has emerged into the popular press. Such research impacts greatly upon the potential for biocide use to select for antibiotic resistance. It has now been clearly demonstrated that Triclosan does indeed possess multiple, disparate targets that include the enoyl reductase of *E. coli*. Numerous bacteria isolated from the mouth, skin and domestic drains have been used to test biocides including not only Triclosan, but also quaternary ammonium compounds and biguanides. It has so far proved impossible to select laboratory-acquired Triclosan resistance in any organism other than *E. coli*, suggesting that in most other bacteria highly conserved targets other than the enoyl reductase are more sensitive and critical to the action of Triclosan. Isoniazid- resistant *Mycobacterium tuberculosis*, whilst mutated in its enoyl reductase, remains exquisitely sensitive towards Triclosan. Long-term microcosm studies of the oral cavity and of kitchen sink drains (a major outlet for consumer products – see Fig. 1) exposed for several months to sub-lethal and use-levels of antibacterial products, including those containing Triclosan, failed to select for isolates with altered susceptibility either towards biocides or to antibiotics. Rather, pre-existing insusceptible species became clonally expanded, and in the drain studies degradative partnerships that utilized Triclosan became dominant. Field studies, conducted both in hospital and domestic settings, comparing areas and households with high and low biocide use, failed to demonstrate any link between biocide use and the antibiotic susceptibility profiles of the isolated bacteria. Further, constitutive hyper-expression of efflux pumps was shown to impose a substantial fitness-cost upon the organisms, rendering their proliferation in 'real-world' microcosms unlikely.



ABOVE:
Fig. 1. Biofilm material excised from a domestic drain (a) and after culture for several months in a constant depth film fermenter (b and c). The photomicrograph in (d) is a montage through the 5 mm deep biofilm developed in (c). The drain microcosm has enabled domestic drain communities to be accurately reproduced in the laboratory (McBain *et al.*, 2003, *Appl Environ Microbiol* **69**, 177–185) and the effects of long-term exposure to antibacterial formulations to be investigated (McBain *et al.*, 2003, *Appl Environ Microbiol* **69**, 5433–5442; McBain *et al.*, 2004, in press).
COURTESY A.J. MCBAIN & S.A. HUWS

Conclusion

With hindsight the risks associated with the profligate use of biocides have been overstated, but the coverage in the lay press has led to a general reaction against various uses of hygienic products. This has extended beyond domestic applications to some medical products used in wound care. It is now imperative that confidence is restored in products that form an essential part of domestic and hospital hygiene. Hygiene should be emphasized and targeted towards those applications where there is demonstrable benefit (food preparation, care of the elderly and immune-deficient, wound care, infection control). Where possible, biocidal formulations that leave no biologically active residues should be chosen. These include strong oxidizers such as bleach and oxygen-generators and alcohols. Live, but let the pathogens die.

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New drugs by manipulating *Streptomyces* genes

David Hopwood

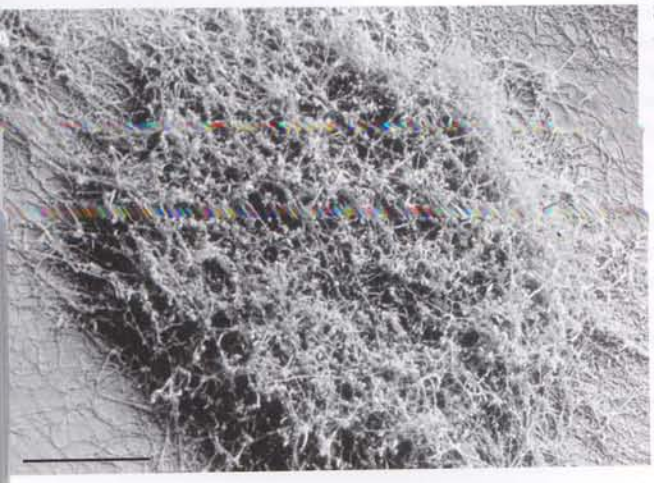
Now that the 'golden age' of antibiotics is over, scientists are developing different ways of making new drugs. David Hopwood describes some of the applications of modern genetics in the search for new antibiotics from *Streptomyces*.

Actinomycetes as antibiotic producers

Ask a typical patient in the doctor's waiting room to name an antibiotic and the chances are it will be penicillin. The development of this product of Alexander Fleming's mould into a wonder drug following the pioneering work of Howard Florey and Ernst Chain at Oxford in the early 1940s revolutionized the treatment of staphylococcal and streptococcal infections and saved countless lives. Numerically, though, the major producers of antibiotics are a group of soil microbes that shot to fame from relative obscurity after the 1943 discovery of streptomycin by Selman Waksman's group at Rutgers University in New Jersey. Streptomycin was the first effective treatment for tuberculosis. It is made by *Streptomyces griseus*, the type species of a large genus within the actinomycetes, later shown to be true bacteria rather than, as earlier supposed, a group intermediate between fungi and bacteria (or even actual fungi). Their growth in the form of elongated branching cells that produce chains of spores for dispersal and dormancy, like a fungus on a tiny scale (Fig. 1), confused early microbiologists, but it is a superficial resemblance.

Penicillin and streptomycin ushered in the antibiotic era that transformed the management of infectious disease. Their discovery was followed in the 1950s and 1960s by the finding of many further antibacterial drugs, including cephalosporin from a fungus, but the majority from the actinomycetes, such as the tetracyclines, erythromycin, kanamycin and vancomycin. Antifungal agents like candicidin and amphotericin were also found, as well as anticancer drugs like doxorubicin and bleomycin. This period was dubbed in retrospect the Golden Age of antibiotic discovery because it was followed by decades in which far fewer useful natural products were discovered, although the antiparasitic compound avermectin was a big success for the treatment of worm and warble fly infestations of livestock, and had a human application to prevent river blindness, caused by a microscopic worm, in Sub-Saharan Africa. It was joined by important immunosuppressant drugs for controlling organ transplant rejection such as cyclosporin from a fungus and tacrolimus from an actinomycete.

BELOW:
Fig. 1. Scanning electron micrograph of a whole *Streptomyces* colony on an agar plate. Note the vegetative mycelium foraging for nutrients at the margin of the colony and the sporulating aerial mycelium piled up in the centre of the colony. Bar, 100 µm.
COURTESY KIM FINDLAY, JOHN INNES CENTRE

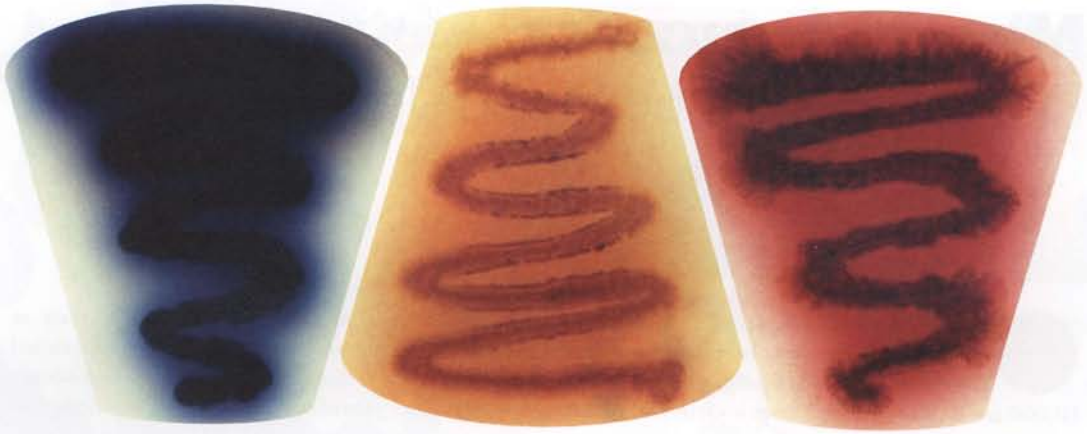


Needs for new antibiotics

With so many successes, why could we possibly need new antibiotics? There are several reasons, including the hope of finding less toxic anticancer agents and drugs for new applications, but the most urgent is the rise of acquired antibiotic resistance. Almost as soon as antibiotics were introduced into medicine the bacteria fought back. They have evolved over countless millions of years to survive the insults of their environments, and they could readily combat the threat posed by clinically used antibiotics. The huge numbers that bacterial populations achieve in a small space and in a short time help them mutate to survive, though the main source of medically important resistance is not fresh mutations, but genes conferring drug resistance transferred into them by mating with non-pathogenic relatives. The ultimate source of resistance to many antibiotics is almost certainly the antibiotic-producing organisms themselves, since they need to have genes for protection against suicide by their own antibiotics. The most famous resistant pathogen is MRSA – methicillin-resistant *Staphylococcus aureus* – that is responsible for much hospital-acquired post-surgical infection. Others include vancomycin-resistant *Enterococcus* in abdominal surgery, and multi-drug-resistant *Mycobacterium tuberculosis*. Another growing problem is resistant Gram-negative respiratory pathogens. There is no doubt that antibiotic over-use and misuse have greatly exacerbated the problem of acquired resistance, but at some level it is an inevitable consequence of even sensible antibiotic use itself.

New antibiotics through genetic engineering

How are we going to find new treatments if the supply of naturally produced antibiotics has been exhausted, or at least if antibiotic discovery became subject to a law of diminishing returns after the Golden Age? One answer has been to go back to the roots of the pharmaceutical industry before the antibiotic era and apply synthetic chemistry to the task of making new drugs. This endeavour, aided by modern developments in robotic synthesis – combinatorial chemistry – has been heavily backed by the big drug companies, so far with little tangible success, but it is still early days. Another is to harness the enzymes that microbes have evolved to make complex molecules with precise stereochemical structures of the kinds that interact specifically with cellular targets, but in new ways. This is the field of combinatorial biosynthesis of 'unnatural natural products', so called because the compounds are made by microbes, and so are 'natural', but not by those making them in the wild, hence 'unnatural'. It builds on knowledge about the genetics of the actinomycetes that has developed over the decades since the mid-1950s, reaching an advanced enough stage for the rational genetic manipulation of antibiotic biosynthesis around 1990. The key requirements were the ability to introduce DNA artificially into the organisms, thus allowing precise genetic engineering, and sufficiently detailed



ABOVE LEFT:
Fig. 2. *Streptomyces* cultures making the blue antibiotic actinorhodin, the brown antibiotic medermycin and the hybrid antibiotic mederrhodin.
COURTESY HELEN KIESER, JOHN INNES CENTRE

knowledge about the organization and roles of the sets of genes that control antibiotic production.

DNA is not taken up naturally by *Streptomyces* as it is by some bacteria, so an artificial procedure is used. The cell walls are stripped off with lysozyme to make protoplasts, still surrounded by the delicate cell membrane. When DNA is added, together with polyethylene glycol to cause the protoplast membranes to coalesce, many of the DNA molecules end up inside the protoplasts, which can regenerate the cell wall and resume normal growth on suitable culture medium. In this way, genes can be added to the recipient's genetic complement or, by allowing the introduced DNA to replace segments of the recipient's genome, deleted from it. This is the basis of genetic mix-and-match experiments in which genes for similar but not identical biosynthetic pathways from different wild strains can be recombined. The first example of making a hybrid antibiotic in this way capitalized on the natural colours of the antibiotics: some of the genes for a blue antibiotic were introduced into a strain making a brown compound, whereupon a purple hybrid was produced (Fig. 2). Nowadays, DNA is often introduced more efficiently by mating from *Escherichia coli*, the laboratory workhorse for molecular genetics. New combinations of genes can be made quickly in a broad-host-range plasmid in *E. coli* and then transferred to *Streptomyces* for antibiotic biosynthesis, using the specialized biochemistry that has evolved in these hosts to make the building units for these complex molecules.

Chemistry through genetics

This first successful demonstration of hybrid antibiotic production was an academic demonstration, but as knowledge accumulated about how the complex multi-enzyme pathways for one of the most important chemical families of natural products, the polyketides, are 'programmed' to make different members of the family, the field has burgeoned. Complex polyketides like erythromycin, amphotericin, avermectin and tacrolimus consist of a skeleton made from a long carbon chain, decorated and folded in characteristic ways, and are made on protein templates in which a linear arrangement of enzyme sites forms an 'assembly line'. The final structure of the polyketides depends on the number, properties and arrangement of these sites, the equivalent of work-stations along the assembly line, which are determined directly by the DNA sequence of the genes encoding the proteins and so can be read just by DNA sequencing, now that many of the rules have been worked out. Since the changes introduced at each workstation along the protein assembly line are nearly all independent of one another, the number of possible combinations is enormous.

Biotechnology companies like Kosan Biosciences Inc. in Hayward California and Biotica Technology Ltd in Cambridge began by exploring some of this 'structure space' and making semi-random mixtures of genes to generate libraries of novel products. However, combinatorial biosynthesis is never going to compete in sheer numbers of molecules with combinatorial chemistry, even if the 'natural' products are likely to be more interesting biologically. Therefore, the focus has shifted to a more targeted approach in which natural products are altered in predictable ways, guided by prior knowledge of structure–activity relationships of the compounds. For example, carbon chains can be lengthened by introducing new sets of enzyme sites into the protein assembly line, and the pattern of side groups along the carbon skeleton can be altered in many different ways. In other words, it is possible to do complex 'chemistry by genetics', taking advantage of the stereochemical precision characteristic of enzyme-catalysed reactions. It is still relatively early days, but the first products are in phase I clinical trials and excitement is running quite high.

Back to nature?

Meanwhile, the idea that nature's bounty was exhausted during the Golden Age has come under review. With the publication of two complete *Streptomyces* genome sequences over the last couple of years, as well as piecemeal sequencing of antibiotic gene clusters from many other actinomycetes, it is obvious that these organisms are capable of producing much greater numbers of interesting natural products than are found by traditional screening procedures. The trick will be, now that the potential has been realized, to find generic methods to wake up these sleeping genes. It may very well be that we are in for a revival of the field of 'natural natural products', guided by genomics, or at the very least to be able to use the toolbox of new genes discovered by genome sequencing to add to the potential for making 'unnatural natural products'.

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Microbial narcotics

Deborah A. Rathbone and Neil C. Bruce

The microbial metabolism and transformation of alkaloid narcotics such as heroin, morphine and cocaine are attracting the attention of researchers. The results offer some interesting applications, as Deborah Rathbone and Neil Bruce describe.

Alkaloids with their plethora of structural varieties and activities have long intrigued both chemists and biologists. More than 10,000 are known, sourced from a variety of plants, microbes and marine organisms. The definition of an alkaloid has changed over the years as the range has diversified, but essentially they are complex, nitrogen-containing, usually heterocyclic molecules. Many alkaloids are of considerable value in both human and animal medicine. Table 1 gives the main types known and some examples of each.

Other reviews provide a deeper study of the biosynthesis and microbial transformation of the vast array of alkaloids; here, we concentrate on the microbial metabolism and transformation of three of the more notorious alkaloids: morphine, heroin and cocaine, and outline some of the applications that have arisen from our work.

Sources of narcotics

Opium and morphinan alkaloids. The Greek word *opos*, meaning milky juice of plants, effectively describes the white latex material that exudes from a cut unripe seed capsule of *Papaver somniferum*, the opium poppy (Fig. 1). Opium is the condensed form of this latex. It is not a modern substance, being mentioned in cuneiform writing on Sumerian clay tablets from 4000 BC. A papyrus dating back some 3,500 years also suggests its use '*to prevent excessive crying of children*'! The main constituents of opium include alkaloids such as morphine, codeine and thebaine, which are extracted and used directly (or their derivatives) in modern-day medicine, providing a range of analgesic (pain-relieving), antitussive (cough suppressing) or narcotic-antagonist properties. Morphine is the main component of opium, determines psychotropic action and is an effective pain reliever. Diamorphine (heroin) is a semi-synthetic opiate prepared by the chemical acetylation of morphine and finds notoriety as a drug of abuse.

Tropane alkaloids. Cocaine is extracted from the leaves of the coca plant, *Erythroxylum coca*. Traditionally, leaves of *E. coca* were chewed by Andean peasants and workers to reduce hunger pain, giving the strength and endurance to work for many hours at high altitudes. In modern times, *E. coca* is no longer simply a minor crop used by peasants in far-off lands: the cocaine trade has become a huge industry.

Cocaine was first isolated in pure alkaloid form in 1860 by the German chemist, Dr Albert Neimann, from leaves brought to Europe. Over the next 20 years or so, it was used extensively by doctors as a stimulant, a local anaesthetic, and, bizarrely, as a cure for morphine dependence. It could be found in over-the-counter tonics, toothache cures, in medicines and as chocolate-covered tablets until 1916. The popular drink, Coca-Cola, initially developed as a non-alcoholic tonic and cure-all, contained cocaine until as recently as 1904 at around 60 mg per serving.

Table 1. Types of alkaloid

Alkaloid group	Examples	Action
Indole	Strychnine	Poison; bird/mammal/insect control agent
	Vinblastine	Anticancer agent
	Physostigmine	Cholinesterase inhibitor
Isoquinoline	Sanguinarine	Antimicrobial agent
	Naloxone	Narcotic antagonist
	Morphine, codeine	Analgesics
	Pholcodine	Antitussive
Pyridine	Nicotine	Natural insecticide
Pyrrolizidine	Heliotrine	Hepatotoxic agent; teratogen
Quinoline	Quinine	Cardiac therapy
Steroidal	α-Tomatine	Natural antifungal agent
	Jervine	Cardiac therapy; hypertension treatment; teratogen
Tropane	Cocaine	Local anaesthetic; tonic; drug of abuse
	Atropine	Cardiac stimulant
	Scopolamine	Anticholinergic agent; briefly used as a truth drug
	Hyoscyamine	Treatment of Parkinson's disease, GI tract disorders, rhinitis
Miscellaneous	Thiocolchicoside	Analgesic; myorelaxant
	Caffeine	Stimulant

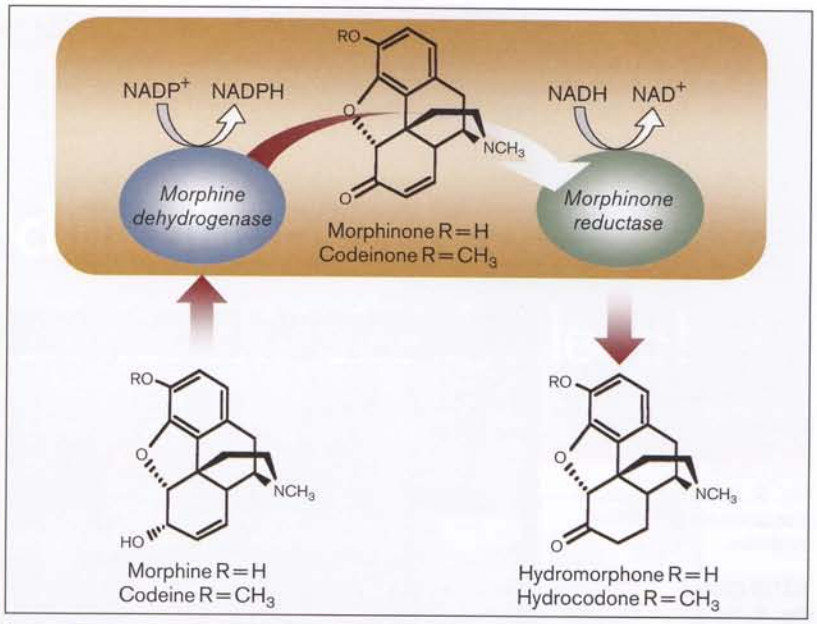
Drugs as a food source

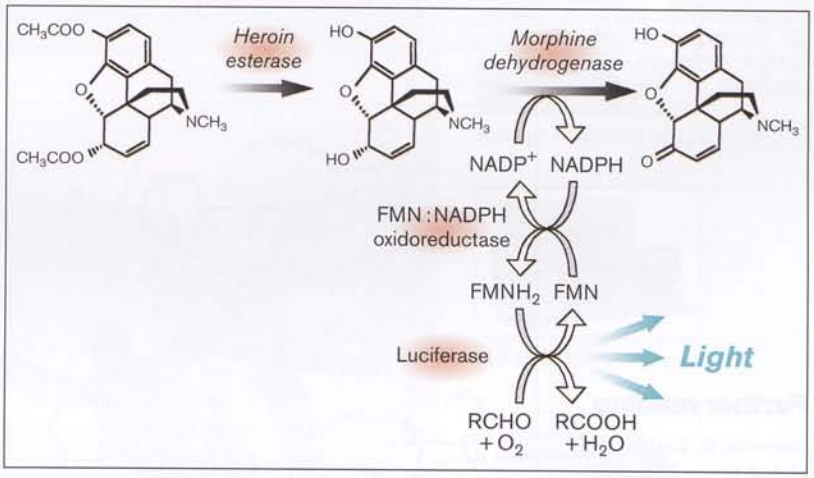
Bacteria are extremely versatile organisms, able to use a whole range of compounds as sources of nitrogen and/or carbon for growth. During the course of research in our laboratory, bacteria were isolated from a range of environmental sources which were capable of growing on morphine, heroin or cocaine. By elucidating the metabolic pathways by which bacteria degrade complex molecules like the morphine alkaloids, we have been able to isolate some novel enzymes with some interesting and useful applications.

Biocatalysis – microbial factories

In the chemical industry a variety of catalysts are needed for well-defined chemical transformations. Often the desired product is available only at low concentrations or as a mixture with unwanted by-products. Costly down-stream purification processes might then make the chemical synthesis economically non-viable or of low yield. An alternative is the use of enzymes or whole-cell biocatalysts. Because of their high stereo- or regio-selectivity, these biocatalysts enable highly specific transformations under moderate reaction conditions.

This is best demonstrated in Fig. 2 which shows a biological system able to convert morphine/codeine to





hydromorphone/hydrocodone. The biocatalyst in this example comprises morphine dehydrogenase (MDH) and morphinone reductase (MR) expressed in *Escherichia coli* JM109. MDH and MR were isolated from *Pseudomonas putida* M10, which was cultured from waste liquors from an opiate processing plant. The products of the biotransformation are valuable pharmaceuticals, hydromorphone being some seven times more potent than its parent compound, morphine; hydrocodone is also used as a mild analgesic. Current methods of manufacturing these drugs are far from satisfactory, requiring protection and deprotection of functional groups and the use of expensive metal catalysts. In addition, low yields or a mixture of products may result, depending on the route taken.

It was possible to improve the initial whole-cell biocatalysis in several ways: first by the incorporation of a soluble pyridine nucleotide transhydrogenase which restored the balance of cofactors; the use of a mutated MDH with improved stability or its replacement with an NAD^+-dependent (3–17)β-hydroxysteroid dehydrogenase which promoted cofactor recycling. The resulting whole-cell biocatalysts were reusable and efficient, giving rise to product yields of up to 90 % in the best cases.

Small changes in chemical structure often result in a drastic alteration of a pharmaceutical property. For example, introduction of an hydroxyl group at the C14 position of morphinan alkaloids dramatically increases their analgesic potency. In addition, C14-hydroxylated morphinans serve as intermediates in the manufacture of narcotic antagonists used to treat respiratory depression following opiate overdose. Such oxyfunctionalization is difficult to achieve chemically, but there are reports of hydroxylated compounds resulting from the incubation of morphine alkaloids with *P. putida* M10 or the fungus, *Cylindrocarpon didymum*.

Biosensor design

Incredibly perhaps in our modern society, heroin was first introduced to the public by Bayer, the pharmaceutical company, as a cough medicine in 1898. There soon followed heroin pastilles, cough lozenges, tablets, water-soluble heroin salts and a heroin/glycerin elixir. At the time, such medicines met the compelling need for an effective treatment for the symptoms of tuberculosis and pneumonia, then the leading causes of death. Heroin, which causes respiratory depression and has a sedative action, allowed a good night's sleep and was seen as a blessing.

The addictive properties of heroin emerged only a year later when researchers reported patients developing tolerance to the drug. Over 100 years later, the fascination with heroin still exists, but addiction to this and other Class A drugs stimulates the majority of crime which pervades our society. There is little/no production of heroin in the UK; instead traffickers bring in small quantities concealed about/in their person or larger bulk hidden inside vehicles, or disguised in any number of ways as legitimate goods such as machinery or chess pieces. Current detection systems available to the Customs Officer often require training or are cumbersome or expensive. The need for a reliable, portable sensor to detect heroin has never been greater.

Selective enrichment of bacteria by growth on heroin as sole carbon source led to the isolation of *Rhodococcus* sp. H1. This organism possesses an inducible heroin esterase which sequentially cleaves the two acetylester groups from heroin to yield morphine. By coupling heroin esterase to MDH, the NADPH liberated in the presence of heroin (or morphine) could then be coupled to a light

TOP LEFT:
Fig. 1. Illustration of *Papaver somniferum* taken from Thomé – *Flora von Deutschland, Österreich der Schweiz* (1885).
COURTESY KURT STÜBER (WWW.BIOLIB.DE)

ABOVE (TOP):
Fig. 2. Conversion of morphine or codeine using a recombinant biocatalyst. Morphine dehydrogenase and morphinone reductase were isolated from *Pseudomonas putida* M10 and expressed in *Escherichia coli* JM109. Whole cells were able to transform morphine/codeine into valuable pharmaceutical products.
COURTESY DEBORAH RATHBONE

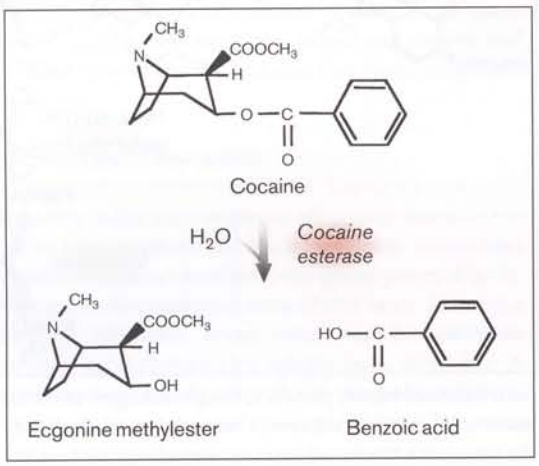
ABOVE (BOTTOM):
Fig. 3. Enzymic detection of heroin. Bacterial heroin esterase and morphine dehydrogenase are coupled with a light output system involving bacterial luciferase allowing the detection of a few particles of heroin.
COURTESY DEBORAH RATHBONE

TOP RIGHT:
Fig. 4. Authentic street samples of heroin compared with pharmaceutical-grade heroin and morphine.

LOWER RIGHT:
Fig. 5. The enzymic conversion of cocaine to non-psychoactive metabolites.

BOTTOM RIGHT:
Fig. 6. The structure of cocaine esterase from *Rhodococcus* sp. MB1. Structure made with Protein Data Bank coordinate file 1JU3 using PyMOL.

ALL COURTESY DEBORAH RATHBONE



output system (Fig. 3). A lab prototype device was able to detect the presence of one or two particles of heroin, and correlated well with authentic samples of drug-containing urine and seized street samples (Fig. 4).

Therapeutics

A strain of *Rhodococcus* MB1 was isolated from rhizosphere soil surrounding the cocaine-producing plant *Erythroxylum coca*. The bacterium contained an esterase which was able to cleave cocaine into ecgonine methyl ester and benzoate (Fig. 5).

Whilst antibody-based therapies are suitable for the more extended periods of time required for cocaine addiction rehabilitation, a more rapid detoxification is vital in an emergency situation such as an overdose. Since cocaine esterase exhibits the fastest reported hydrolysis of cocaine into non-psychoactive metabolites, it has a valuable potential therapeutic application as an intravenous treatment for cocaine overdose.

The crystal structure of cocaine esterase has recently been solved (Fig. 6); it is the first structure of a cocaine-degrading enzyme to be reported. A thorough understanding of the structure–function relationship of this enzyme, which such data allows, provides vital information required for the generation of more efficient cocaine antibody catalysts.

Summary

By exploiting the metabolic versatility of microbes, it is possible to isolate novel enzymes whose properties make them attractive for a variety of applications such as biocatalysis, biosensor design and therapeutics to name but a few. The rapid advancement of recombinant technologies has already allowed for their improvement and points the way towards a new generation of valuable and sustainable resources.

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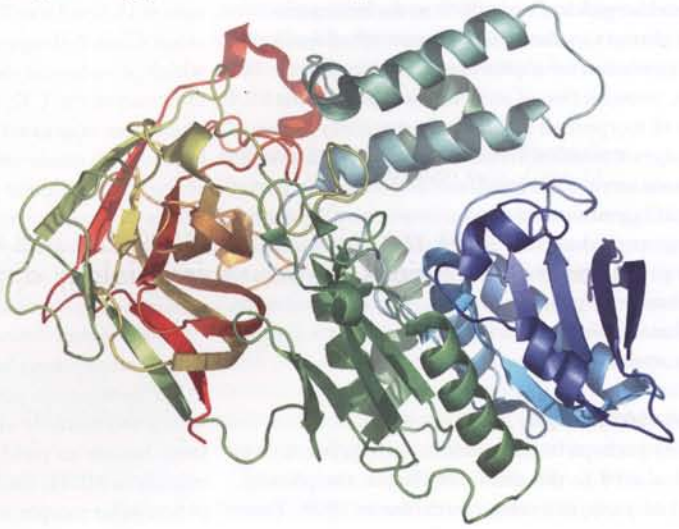

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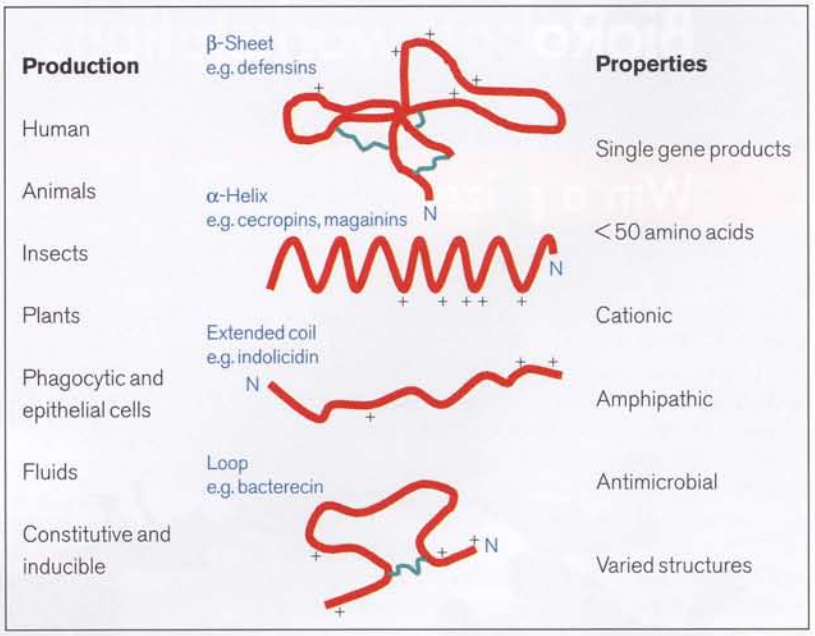
Host defence peptides

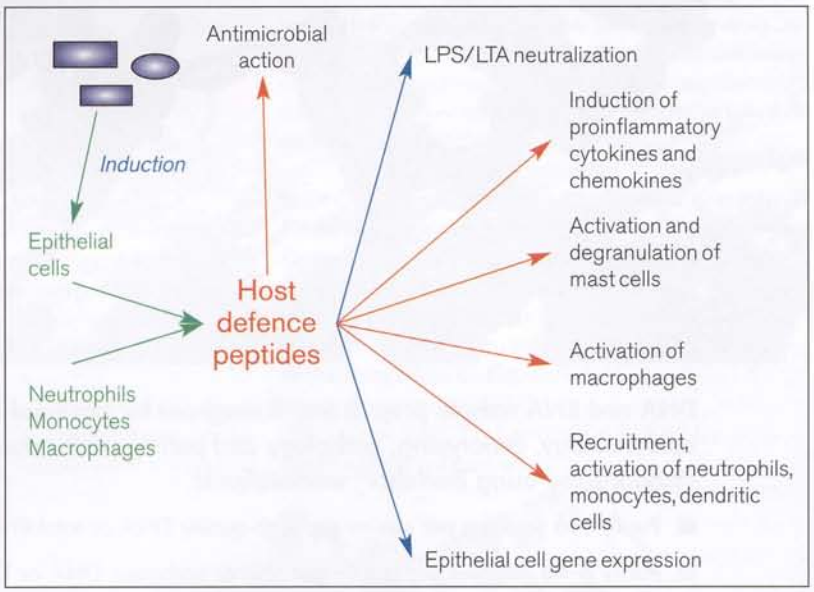
Deirdre Devine

Host defence peptides, also known as antimicrobial peptides, are a diverse group of small peptides that have emerged as exciting multifunctional components of the immune system, as well as being promising new anti-infective agents.

Host defence peptides (HDPs, Fig. 1) are low-molecular-mass single-gene products that are cationic, amphipathic, and exhibit varied activity against a range of Gram-positive and Gram-negative bacteria, fungi and viruses. Well over 500 naturally occurring HDPs have now been described. Their potential applications were recognized decades ago with the discovery of magainin in frog skin secretions, which led to the establishment of the first company (Magainin Inc.) aiming to develop such peptides as therapeutic agents. In the last 10 years, interest in their biology has increased enormously with the discovery that, not only are they antimicrobial, but they are also immune modulators (Fig. 2).



TOP RIGHT:
Fig. 1. Properties and production of host defence peptides.



BOTTOM RIGHT:
Fig. 2. Multiple activities of HDPs. The recorded activities of HDPs extend beyond antimicrobial action to functions indicating roles in regulating and linking host defence mechanisms. Some activities (red arrows) are involved in enhancing an acute inflammatory response and/or in signalling between innate and cellular adaptive immune responses. Others (blue arrows) serve to downregulate a cellular inflammatory response. Neutrophil defensins are also known to promote wound healing and related functions as they induce syndecan production, are mitogenic for fibroblasts and epithelial cells, stimulate growth of fibroblasts and promote apoptosis and clearance of infected cells.

Production of HDPs

Although HDPs are structurally diverse, their function has been conserved. Higher and lower organisms, from insects and plants to humans, produce a range of these peptides as part of their first-line innate defences, within phagocytic cells or at epithelial surfaces. At each site of production, HDPs form part of a cocktail of antimicrobial substances which *in vivo* work synergistically to combat infection.

Most tissues appear to be protected by a specific array of epithelial peptides which are produced constitutively or are induced by proinflammatory cytokines and by exposure to micro-organisms. In humans and many other animals the β-defensins (BDs) are particularly important epithelial HDPs. Recent genome sequence data analyses have shown that humans and mice possess > 20 and > 40 putative BD genes, respectively. Some peptides, such as human BD1-3 and cathelicidin LL-37, provide protection at a number of sites, but others are specialized, e.g. some mammalian epididymal peptides, hepcidin in human liver and urine, and histatins in human salivary glands. HDPs are amenable to considerable diversification and evolutionary studies have indicated that varied peptides have arisen through rapid evolution in response to the positive pressure of colonizing micro-organisms. Isoforms of a number of HDPs, differing by a few terminal amino acids, have been isolated from natural fluids or tissues. These minor differences produce significant changes in antimicrobial activity, providing an additional mechanism to ensure maximal and optimal antimicrobial cover at a specific site, with little metabolic cost to the host cell.

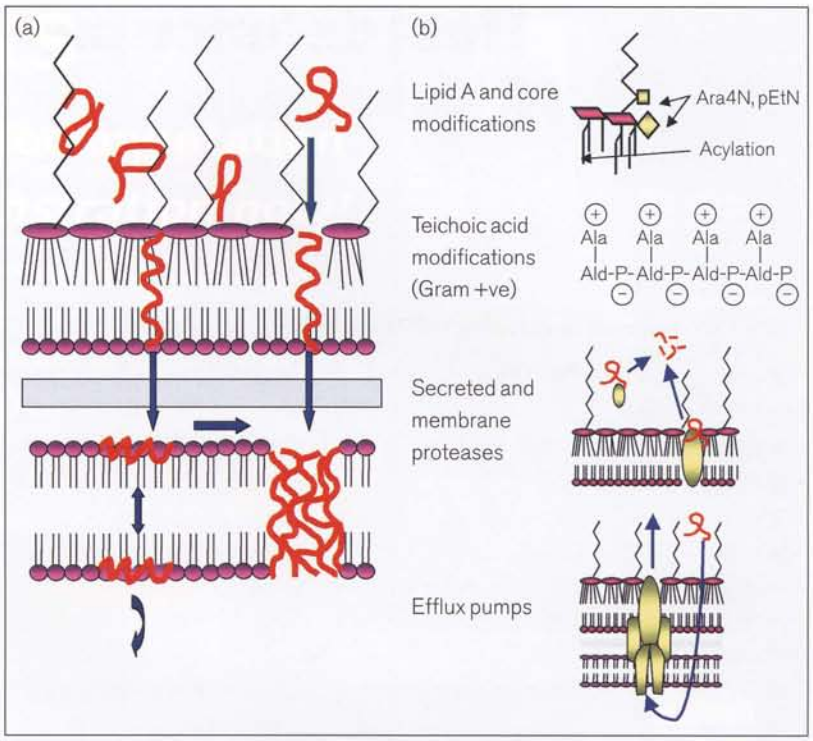
Antibacterial activity

HDPs bind avidly to charged bacterial cell-wall components, particularly lipopolysaccharides (LPS) and lipoteichoic acids (LTA), and are able to depolarize and permeabilize membranes (Fig. 3). Some bacteria are innately resistant to HDPs, for example *Pseudomonas aeruginosa* and *Burkholderia cepacia*. This is related to the LPS structures of these organisms, which have properties reducing the charge interactions with HDPs. In particular, substitutions of lipid A and core phosphate residues with 4-deoxy-4-aminoarabinose (Ara4N) cause partial charge neutralization, and addition of palmitate to lipid A results in alterations to membrane fluidity and self-promoted uptake of HDPs. *Salmonella enterica* serovar Typhimurium increases in pathogenicity through LPS modifications, including addition of Ara4N and palmitate, under the control of two-component signal transduction pathways (*phoPQ* and *pmrAB*). Interestingly, these LPS modifications can change other host–microbe interactions, e.g. binding to Toll-like receptors. Other modifications carried out by bacteria that alter interactions with HDPs include decoration with host-derived phosphorylcholine and modification of teichoic acids by D-alanine. Many of these modifications are carried out by both pathogenic and commensal bacteria.

The activity of many purified HDPs is inhibited by physiological salt concentrations. Some have suggested that the cystic fibrosis (CF) defect in ion transport results in tracheal exudates with high concentrations of NaCl, thereby inactivating HDPs and allowing pathogenic bacteria to infect people with CF. This is contentious as not all studies have confirmed high NaCl concentrations in airway fluids and it is a paradox that organisms like *B. cepacia*, which are naturally resistant to HDPs, should require salt-inactivation of these innate defences to express their pathogenicity.

Other functions in immune responses

HDPs are multifunctional molecules (Fig. 2) that are now thought to be of fundamental importance in host defence, serving as signalling molecules communicating between the innate and adaptive immune systems. Their multiplicity of function has led to the proposal that they should most accurately be described as HDPs (or peptides of the innate immune system) rather than as antimicrobial peptides. Some of their activities are involved in enhancing an acute inflammatory response, but they can also inhibit such responses, either through sequestration of effector molecules like LPS and LTA or through direct action of the peptide on host-cell gene expression. Some of the most exciting recent developments in this area have revealed roles for HDPs in signalling between innate and cellular adaptive immune responses. Thus, in addition to regulating cytokine production, α- and β-defensins attract immature dendritic cells and memory T cells, promoting an adaptive immune response. α-Defensins also enhance proliferative responses of T cells, promoting systemic IgG and IgM production. The use of gene microarray technology to dissect changes in global gene expression in host cells is greatly facilitating our understanding of the activities of these multifunctional immunomodulatory molecules.



ABOVE:
Fig. 3. Interactions between HDPs and bacterial cells. (a) Mechanism of antibacterial action. Peptides bind to divalent cation-binding sites and associate with the polyanionic outer moieties of LPS, disrupting and expanding the outer membrane and allowing passage of HDPs through the outer membrane. HDPs then bind to the interfacial region of the cytoplasmic membrane. When at sufficient concentrations, HDPs aggregate within the membrane, causing depolarization and permeabilization. Some monomers may detach and gain access to the cytoplasm. (b) Mechanisms of resistance to HDPs. In addition to lipid composition of the cytoplasmic membrane and the presence of an electrochemical potential across this membrane, resistance to HDPs may be determined by charge density and structure of LPS and other cell-wall components, responses of bacterial cells to environmental changes and stresses, and peptide breakdown and efflux mechanisms.

Development as therapeutic agents

Because of their broad spectrum activity and the ability to design a multitude of analogues with altered activities from one molecule, naturally occurring HDPs are providing templates for the development of novel anti-infective agents. They have a major advantage in that resistance to HDPs appears to develop slowly, if at all. Although the first magainin peptide to reach Phase III clinical trials fell at this hurdle, many biotech companies are actively developing HDPs for topical and systemic use (Table 1). Their immunomodulatory and potential anti-inflammatory properties are being exploited by a recently established Canadian company, Inimex.

In vivo importance

There is little doubt that HDPs are significant in defence against infection. In humans and mammals, concentrations of neutrophil and epithelial HDPs increase to significant levels following infection or injury. Resistance to neutrophil HDPs has been cited as a pathogenicity determinant for intracellular or invasive pathogens, such as *S. enterica* serovar Typhimurium and group A streptococci. Studies of rodents have supported a role for HDPs in defence against infection and they demonstrate peptide redundancy (or overlap of function of multiple HDPs expressed at one site) in host innate defences, and suggest differences in the roles of the same peptide at different sites.

In addition to being assaulted by potential pathogens, many body sites are colonized by large numbers of diverse commensal micro-organisms, which contribute to normal development and protection of the host and

Table 1. Companies developing HDPs as therapeutic agents

Company	Peptides	Treatment
Clinical trials		
Magainin Inc.	Locilex™	Impetigo; diabetic foot ulcer
Intrabiotics	IB 367	Oral mucositis; CF lung infection
Micrologix	MBI 226, MBI 594N	Central venous catheter infection; acne
Xoma	Neuprex	Meningococcaemia; endotoxaemia
Demegen	P113 D2A21	Gingivitis Wounds and burns
Pre-clinical		
AM-Pharma	Histatin- and lactoferrin-based	Hepatitis C; multiply resistant bacteria
Demegen	P113D P113L	CF lung infection Oral candidiasis
Helix BioMedix	HB107 HB50	Burns Wounds, skin infections
Inimex	Various	Immunomodulation

are usually tolerated without eliciting a detrimental inflammatory response. HDPs produced by phagocytic and epithelial cells possess characteristics indicating they are central to selection and regulation of both pathogenic and commensal micro-organisms: (i) they are diverse, host-species-specific and site-specific; (ii) they appear to have evolved in response to selection pressures exerted by resident and pathogenic microbial populations; (iii) they kill micro-organisms and/or provide signals regulating effective innate immunity and linking the innate and adaptive immune responses. Whilst experimental examination of the role of HDPs in host–microbe relationships is challenging, it is apparent that pathogenic and commensal organisms use similar, but varied, strategies to resist or evade HDP activity, allowing colonization and survival on host mucosa. In addition to interacting with whole microbial cells, these peptides bind to microbial molecules such as LPS and LTA, and may function in concert with other innate defence molecules to minimize and regulate immune responses at mucosal sites assaulted by large numbers of bacteria and their released cellular components. Thus, HDPs help maintain host–microbe homeostasis and ensure appropriate host responses to bacteria and their cellular products.

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The voice of young scientists in the media

17 September 2004, 11am–4pm

At the Science Media Centre, Royal Institution, Albemarle Street, London W1S 4BS.

Sponsored by:
The Health and Science Communication Trust
The Royal Pharmaceutical Society of Great Britain
The Society for Endocrinology
The Society for General Microbiology

This free event is for young scientists who are passionate about science and want to take on the challenge of communicating evidence-based research to a wider audience. It combines a discussion about science-related controversies in media reporting, with practical guidance and skills to help younger scientists make a greater contribution to such debates.

Sessions:

- *Science in the media*
  Participant discussion on the changing image and role of science and scientists in the public domain. What happens when research announcements go wrong; statistics are manipulated; risk factors are distorted; or the discussions become polarized?
- *What journalists are looking for*
  A panel of journalists – Mark Henderson (*The Times*), Tom Feilden (BBC R4, *Today* programme) and Anna Fazackerley (*Times Higher*) – will explain how they approach stories and balance the need for news and entertainment with reporting science, and answer questions.
- *Taking a realistic approach to science reporting*
  How scientific news is communicated, typical difficulties, and areas of misunderstanding. The Science Media Centre will outline practical guidance for young scientists to get their voices heard in debates about science, including writing articles and letters, and providing comment.

If you are a postgraduate student, a post-doctoral fellow, or equivalent in your first job, and you would like to attend, please send a short CV and covering letter to Ellen Raphael by **31 July 2004** (email enquiries@senseaboutscience.org; or post to Sense About Science, 60 Cambridge Street, London, SW1V 4QQ). Please note there are only 40 places available and earlier applications are more likely to be successful.

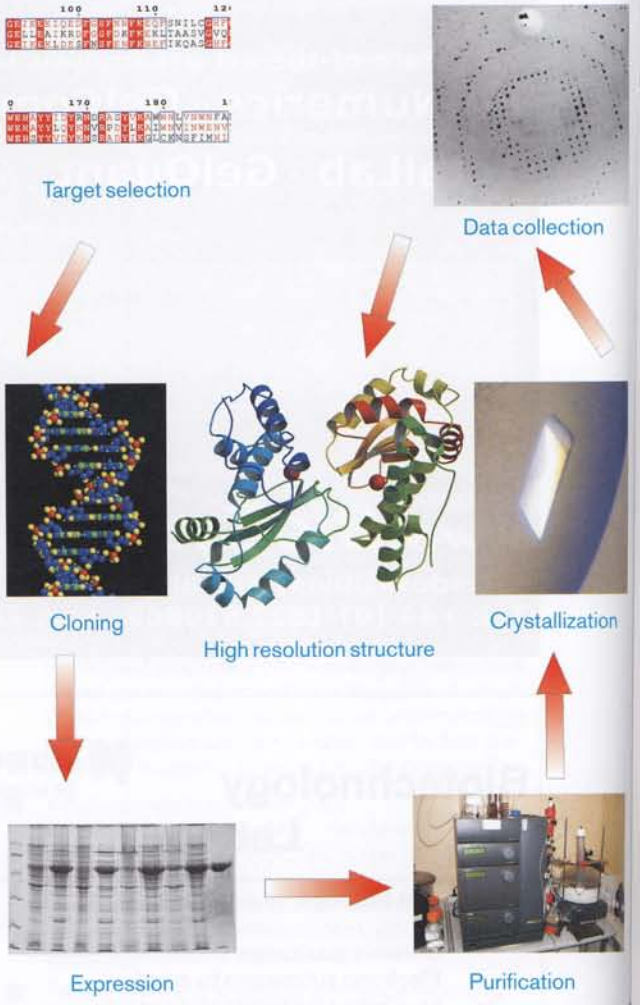
SENSE ABOUT SCIENCE

For further information visit
www.senseaboutscience.org
or phone Ellen Raphael on 07730 941414.

Structural pathogenomics

Ian Boucher, Jim Brannigan, Mark Fogg and Claudia Schnick

Structural genomics uses the information gleaned from genome sequencing to determine structures of the gene products. A 'structural genome' implies a complete 3-D description of every protein in an organism. Experimentally, this will prove difficult, as each protein is unique – unlike DNA, which is tractable for sequence analysis regardless of its source. However, proteins can be described by a finite number of representative structural 'folds' and useful 3-D models can be built if the protein shares a fold of known structure. This promises a structural metagenome, where all protein structures can be modelled. The huge task of generating the fold library requires a multidisciplinary effort, which has led to a number of consortia that collaborate to churn out structures by nuclear magnetic resonance, X-ray crystallographic and computer modelling techniques. The structural genomics community has dedicated a lot of effort to the development of high-throughput, automated techniques for the workflow (Fig. 1), and some groups focus on the analysis of pathogenic organisms (Table 1).



RIGHT:
Fig. 1. The structure determination process is being speeded up by optimizing and automating each step, such as bioinformatics, protein production and purification, for high-throughput. Techniques such as crystallization on a nano-scale, automation of crystal handling and data collection at synchrotron beamlines, as well as novel methods for solving structures are being developed by the structural genomics community.
The structure shown is an Fe-dependent superoxide dismutase from *P. falciparum* – an important enzyme for the malaria parasite's response to oxidative stress – which has been solved in York.

Cherry-picking targets for new antimicrobials

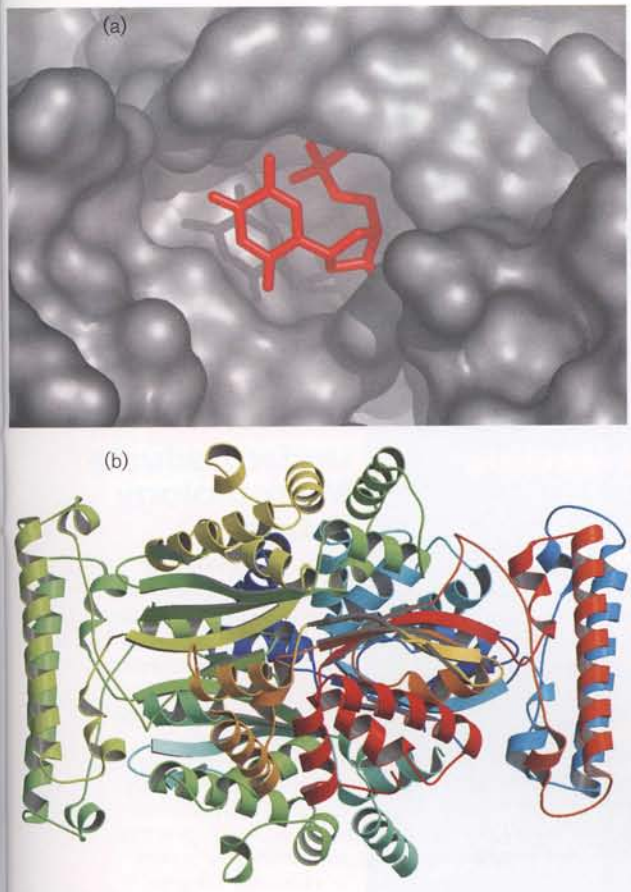
As well as identifying proteins implicated in pathogenesis, the analysis of genome sequences can suggest specific metabolic pathways and enzymes representing weak points in the pathogen's defence and survival strategies. Proteins essential for the viability of the pathogen, which are absent or significantly different to their human counterparts, are likely to be good candidates for antimicrobials. As an example, the causative agents of malaria (*Plasmodium falciparum*, www.plasmoDB.org) and tuberculosis (*Mycobacterium tuberculosis*), together responsible for an estimated 5 million deaths per year, share a fatty acid biosynthetic pathway that is not found in humans. Screening has identified compounds that are active against a key enzyme, enoyl reductase, in this metabolic pathway. The X-ray structure of the *Mycobacterium* enzyme with one of these compounds elucidates the binding characteristics that can be further exploited for drug optimization and so provide a powerful tool in fighting both malaria and tuberculosis.

Structural genomics is also providing structures of proteins that identify new targets for drug intervention. These include essential proteins of currently unknown function, and proteins whose biological functions have been illuminated by the structure. For example, the Joint Centre for Structural Genomics in California has uncovered thymidylate synthase complementing protein (TSCP) as a potential drug target. Blocking TSCP prevents bacteria from synthesizing new DNA, leaving the human thymidylate synthase enzyme unaffected.

Table 1. Selected structural genomics projects

For a full list, see relevant links at the International Structural Genomics Organization (**www.isgo.org/list/list.html**) and the PDB (**www.rcsb.org/pdb/strucgen.html**).

Structural Genomics of Pathogenic Protozoa Consortium	depts.washington.edu/sgpp
Tuberculosis Structural Genomics Consortium	www.doe-mbi.ucla.edu/TB
Berkeley Structural Genomics Center	www.strgen.org
Midwest Center for Structural Genomics	www.mcsg.anl.gov
Keck Center for Microbial Pathogens	depts.washington.edu/keckcmp
Structural Proteomics in Europe (SPINE)	www.spineurope.org
Northwest Structural Genomics Centre	www.nwsgc.ac.uk
Joint Center for Structural Genomics	www.jcsg.org
New York Structural Genomics Consortium	www.nysgrc.org
Structure 2 Function Project	s2f.carb.nist.gov
RIKEN Genomic Sciences Center	www.gsc.riken.go.jp
BIGS	igs-server.cnrs-mrs.fr/Str_gen/



LEFT:
Fig. 2. (a) Solid surface representation of the TSCP active site pocket, showing the ligand (in red liquorice) and area for potential drug design. (b) 3-D structure of TSCP from *Thermotoga maritima* showing the α-helix and β-sheet secondary structures.
SEE WWW-SSRL.SLAC.STANFORD.EDU/RESEARCH/HIGHLIGHTS_ARCHIVE/TSCP.HTML

What next? Structure-based drug discovery

The high-resolution structure to 1·6 Å of the TSCP enzyme has allowed the arrangement of the active site to be investigated at a level of detail that would not be possible with a modelled structure. This precision makes knowledge-based drug design a powerful tool (Fig. 2). Small molecules likely to bind to the protein can be tested in an experimental or a virtual way. Computer-based *in silico* screening involves large chemical libraries and a variety of docking or scoring tools being applied to find favourable interacting partners with the protein target. The virtual approach has, of course, to be verified experimentally, by co-crystallization of candidate compound and protein, and eventually by testing the inhibitory effect in living cells. A list of drug targets with inhibitors designed using structure-based drug discovery methods, and a lot more information about high-throughput structural biology can be found on the website of the Stevens Laboratory, Scripps Research Institute (stevens.scripps.edu/webpage/htsb/).

More speed, less waste

Just as the techniques for sequencing DNA have evolved to meet the need of large-scale projects, developments fuelled by structural genomics will serve the biological community as a whole in the headlong rush for more structures at a scale and speed undreamed of just a few years ago. The Protein Data Bank (PDB, www.pdb.org), a public repository for structural data held only seven structures in 1971. After 25 years, it grew to just over 5,000 entries, which is approximately how many were deposited during 2003 alone!

In February 2003, a previously unknown virus was isolated in patients suffering from severe acute respiratory syndrome (SARS). By May, the complete viral genome and all its RNA transcripts had been mapped and sequenced, revealing a coronavirus (SARS-CoV) encoding 28 mature proteins. Whilst the imperative was to detect and contain the virus, protein structure centres around the world quickly took up the challenge to produce structures of SARS-CoV proteins, to identify possible drug targets and directly combat the infection. The first homology model of a SARS-CoV protein was published in *Science* in June, suggesting that the currently available inhibitor of rhinovirus (common cold), 3C protease, could be modified to be useful against the SARS-CoV homologue. Members of the Structural Proteomics in Europe (SPINE) consortium were also on the hunt for experimental structures. A paper demonstrating the first crystallization of a SARS-CoV protein (replicase nsp9) was submitted in July 2003 and the final structure was presented in February 2004. So, in less than a year (with the earliest useful results available within a few weeks), an unprecedented international effort managed to identify a previously unknown infectious disease, sequence its genome and elucidate structures of its proteins to give potential drug targets.

How can we make the most of it?

Since many laboratories work on similar approaches to examine pathogen enzymes, it is essential that an information flow supports the work in a co-operative manner. Most of the structural genomics projects provide open access to their strategies, target lists and the state of progress. The PDB has created a centralized target registration database for structure projects worldwide (TargetDB) to show the current status and tracking information for new protein structures. In this way, the increasing amount of data can be used not only by structure laboratories, but also by other groups in an interdisciplinary way. This may be the enduring legacy of structural genomics efforts. Taking the lead from DNA sequencing labs that championed the immediate release of data, freely available structure information will, hopefully, speed up the process of finding effective ways to control diseases that threaten the lives of many.

Ian Boucher is supported by a BBSRC studentship. Jim Brannigan and Claudia Schnick are funded by the Wellcome Trust on a Malaria Functional Genomics Grant. Mark Fogg is funded by the EU through the SPINE network, and works on the human pathogens* Campylobacter jejuni *and* Bacillus anthracis. *The York lab also has links to the TB consortium.*
Structural Biology Laboratory, University of York, York YO10 5YW, UK.
Tel. 01904 328271; Fax 01904 328266
**email jab@ysbl.york.ac.uk*

Further reading

Aanand, K. & others (2003). Coronavirus main proteinase structure ($3CL^{pro}$) structure: basis for design of anti-SARS drugs. *Science* 300, 1763–1767.

Campanacci, V. & others (2003). Structural genomics of the SARS coronavirus: cloning, expression, crystallization and preliminary crystallographic study of the Nsp9 protein. *Acta Crystallogr* D59, 1628–1631.

Kuo, M.R. & others (2003). Targeting tuberculosis and malaria through inhibition of enoyl reductase. *J Biol Chem* 278, 20851–20859.

Mathews, I.I. & others (2003). Functional analysis of substrate and cofactor complex structures of a thymidylate synthase-complementing protein. *Structure* 11, 677–690.

Sutton, G. & others (2004). The nsp9 replicase protein of SARS-coronavirus, structure and functional insights. *Structure* 12, 341–353.

www-ssrl.slac.stanford.edu/research/highlights_archive/tscp.html

SocietyNews

February Council Meeting

Industrial Officer post on Council

● Council has been concerned for some time now to increase the relevance of the activities of the Society to and its interactions with industries in the field of microbiology. It has now taken the decision in principle to create an Industrial Officer post on Council and will be developing its views on the role of the position in the coming months.

Recognition for Nobel Laureate

● Council has approved the election of **Sir Paul Nurse** to Honorary Membership of the Society. Sir Paul, who is a Fellow of the Royal Society, was awarded the Nobel Prize for Medicine in 2001 and is currently President of Rockefeller University in New York.

Finance matters!

● Members will be aware that the financial markets have experienced some uncertainty and volatility in recent years and it is important to remember that the stewardship of the society's resources is of crucial importance to its charitable aims. So it was with considerable pleasure that Council received notice that the financial position at the end of 2003 compared very favourably with both the out-turn for the previous year and the projected deficit anticipated for 2003. The modest surplus achieved in 2003 represented a remarkable turn around without any reductions in the Society's activities in support of microbiology. In consequence this was the first year since 1998 that it has been possible to transfer additional funds to the Society's reserves.

More schools sign up

● The Education Officer highlighted to Council the welcome increase in its schools membership, which also coincides with SGM's particularly high profile at the Association for Science Education meeting in Reading in January.

Journals forging ahead

● Council was pleased to hear that the increasing quality of its journals was being reflected in increased submissions of manuscripts – now generally by the online route – a reminder of the importance of these titles to the Society and its activities.

● *Alan Vivian, General Secretary*

2004 Bergey Award

The winner of the 2004 Award is SGM member **Rudolf Amann** of the Max Planck Institute for Marine Microbiology, Bremen, Germany. The award, donated by the Board of Trustees of Bergey's Manual Trust and Springer-Verlag, of a certificate and US$2,000 will be presented at ISME-10 in Cancun, Mexico, in August 2004.

Annual General Meeting 2004

The Annual General Meeting of the Society will be held on **Tuesday, 7 September 2004** at the Society Meeting at Trinity College Dublin. Agenda papers, including reports from Officers and Group Conveners, and the Accounts of the Society for 2003 will be circulated with the August issue of *Microbiology Today*.

Council Officers

Professor Hilary Lappin-Scott, School of Biological Sciences, University of Exeter, has accepted Council's invitation to be the next Scientific Meetings Officer of the Society. She will start her term of office in September and her profile will appear in a future issue of *Microbiology Today*.

Professor Sir John Beringer, Pro-Vice Chancellor of the University of Bristol, is to be congratulated on his appointment by the Prime Minister to the Council for Science and Technology. The extra commitments attendant on this honour have, unfortunately, led to Professor Beringer tendering his resignation as International Secretary. He has kindly agreed to continue in office until Council has appointed a replacement.

Staff News

PHOTO J. WESTWELL, SGM

We were sorry to say goodbye recently on retirement to **Diane James** whose voice will be familiar to many SGM members at the end of the telephone at Marlborough House. Diane has been receptionist since September 1997 and we shall miss her cheerful and efficient services in handling not only the switchboard and greeting our visitors, but also answering membership enquiries and dealing with all the mail. Various celebrations took place to mark both the significant birthday and the retirement, with gifts of garden chairs for that well-earned rest from SGM staff and a gold watch from the Society. We wish Diane every happiness for the future.

News of Members

The Society notes with regret the deaths of **Dr A.H.L. Chamberlain** (Member since 1979), **Dr K.E.K. Rowson** (Member since 1955), **Dr J.G. Shoesmith** (Member since 1954) and **Dr F. Brown** (Member since 1966; see p. 97 of this issue).

Undergraduate Microbiology Prizes

The prizes are intended to encourage excellence in the study of microbiology by undergraduate students and to promote scholarship in, and awareness of, microbiology in universities. The prizes are awarded annually to the undergraduate student in each qualifying institution who performs best in microbiology in their penultimate year of study for a Bachelor's degree. Each winning student will be awarded £100, a certificate and a free year's undergraduate membership of the SGM.

One prize is available to each university in the UK and Republic of Ireland offering an appropriate microbiology course. The university chooses the assessed microbiological work for which the prize is awarded. The submission should be supported by formal marks, not an informal assessment. Winning students should have attained at least 2(I) overall in their degree examinations at the stage at which the award is made.

Eligible students may be registered for any degree with a significant microbiology content (e.g. Biotechnology, Applied Biology, etc.) not just a BSc Microbiology. Universities are now invited to nominate a student for a 2004 SGM Undergraduate Microbiology Prize. Submissions can only be accepted on the form which has been sent to all institutions. The full rules and further copies of the form may be downloaded from the SGM website or obtained from the Grants Office at Marlborough House. The closing date for nominations is **31 August 2004**.

SGM Prize Lectures and Awards

Procedure for nominations

A range of prestigious awards is made by the Society in recognition of distinguished contributions to microbiology. To facilitate nominations, the rules for each prize lecture due to be awarded in 2005 are provided on this page and a form is available overleaf. It is now also possible for self-nominations to be made for all awards. The award panel will consider the submissions in the autumn and their recommendations will be taken to November Council for approval. The outcome will be announced in the February 2005 issue of *Microbiology Today*.

Nominations are now sought for the 2005 prize lectures. Please complete the form overleaf and send it to Professor Alan Vivian, c/o SGM HQ. Professor Vivian will be pleased to discuss the criteria for nominations, should any queries arise.

The closing date for all nominations is **30 September 2004**.

Fleming Award

The Fleming Lecture is awarded annually for outstanding research in any branch of microbiology by a young microbiologist in the early stages of his or her career. The award is £1,000.

1. Nominees should normally have been engaged in research for not more than 10 years after doctoral qualification or equivalent. Years may be added to this total in respect of career breaks, for parenthood or other substantive reasons.
2. There should normally have been a connection with the scientific activity of the Society, either by means of past and continuing membership of the Society (a minimum of 3 years' membership of the Society would normally be expected), or past presentation(s) at a Society meeting or publication(s) in a Society journal, or an organizational or administrative contribution to the scientific work of the Society.
3. Candidates, who need not be members of the Society, should submit an outline CV including details of qualifications, scholarships, research grants obtained, etc., a list of publications, an outline of their career progression (posts held in postdoctoral research) and the names of two members who are familiar with their work, who will be asked to provide a statement detailing the candidate's contribution to microbiology and merit for the award. Alternatively members who wish to make a nomination should provide such a statement and should arrange for a second member willing to support the nomination to provide a statement, and should ask the candidate to provide the CV and publications list.
4. The recipient will be expected to give a lecture based on his or her work to a meeting of the Society, which will usually not be that which takes place in the Spring. He or she may be asked by the Council of the Society to repeat the lecture at another centre in this country or in Europe. Expenses of the lecturer will be paid by the Society. Requests for such a second lecture should be made to the General Secretary and will be considered by Council. The text of the lecture will be published in whichever of the Society's journals is the most suitable. The choice will be at the discretion of the Editors of the journals.
5. In the event of there being no successful nominee in any particular year, the Award money will be returned to the funds of the Society. Any given nominee may be chosen once only.

Colworth Prize Lecture

Awarded biennially for an outstanding contribution in an area of applied microbiology. It is sponsored by the Colworth Laboratory of Unilever Research. The prize is £1,000 and the winner gives a lecture on his or her work. The lecture is usually published in a Society journal.

Nominations shall be made by any two members of the Society: the nominee need not be a member of the Society. Nominations should be accompanied by a statement of the contribution to applied microbiology made by the nominee, supported by reprints or other appropriate documentation. A brief CV of the nominee and a full bibliography of his or her work should also be included. Alternatively, candidates may submit all of the information listed above, together with the names of two members who are familiar with their work, who will be asked to supply the appropriate statement with regard to the candidate's contribution to applied microbiology.

There will be no restriction by reason of age or nationality of those eligible for nomination for the Colworth Prize Lecture. Recipients of the Lectureship may not be nominated on a subsequent occasion.

The recipient of the Colworth Prize Lectureship will be expected to give a lecture based on the work for which the Prize Lectureship has been awarded to a meeting of the Society, normally the Spring meeting following the announcement of the award, and to repeat the lecture at the Colworth Laboratory. The recipient will be strongly encouraged to publish the lecture in whichever of the Society's journals is most suitable. The choice will be at the discretion of the Editors of the journals.

Peter Wildy Prize for Microbiology Education

This is awarded annually for an outstanding contribution to microbiology education.

1. The Peter Wildy Prize of £1,000 shall be awarded annually for an outstanding contribution to microbiology education, without restriction on the area of microbiology in which the award is made. Microbiology education for the purpose of the award need not be confined to university teaching. It may also include education of the general public, school pupils or professional groups.
2. Nominations for the Peter Wildy Prize shall be made by any two members of the Society; the nominee need not be a member of the Society. Alternatively, candidates may submit all of the information listed above, together with the names of two members who are familiar with their work, who will be asked to supply the appropriate statement with regard to candidate's contribution to education.

   Nominations should be accompanied by a statement of the contribution to microbiology education made by the nominee, supported by appropriate documentation if available. A brief CV of the nominee should also be included.
3. There shall be no restriction by means of age or nationality of those eligible for the Prize. Recipients of the Prize may not be nominated on a subsequent occasion.
4. The recipient of the Prize will be expected to give a presentation based on an aspect of educational work for which the Prize has been awarded to a meeting of the Society, normally within a year of the announcement of the award. The presentation may take the form of a lecture, workshop, audio/visual display or any other appropriate activity. The recipient will be strongly encouraged to publish an article based on the presentation in *Microbiology Today*.

Fred Griffith Review Lecture

Held biennially and commemorates the pioneering contributions of Fred Griffith to bacterial genetics. It is awarded in recognition of long and distinguished service to microbiology. The winner receives £1,000 and gives a personal overview of an area of microbiology. The lecture is usually published in a Society journal.

Grants

International Research Grants

The purpose of the grants is to allow scientists to travel to or from the UK and Republic of Ireland to carry out a defined piece of research in any field of microbiology. Applicants must be of postdoctoral level or above. The visits may be from 1 to 3 months duration. The awards cover the costs of return travel, a subsistence allowance and a contribution towards the costs of consumables in the host laboratory. The closing date is **11 October 2004**.

International Development Fund

The fund aims to provide help to countries where microbiology is inadequately developed, but where its further development may assist education or the economy of these countries. At present these include many places in the Far East, Africa, South and Central America, the Indian sub-continent and Eastern and Central Europe. Awards are made by competition to SGM members and support may be available for:

- running short lecture courses and laboratory training in microbiological subjects. Host laboratories are usually expected to provide some evidence of local support for the courses. Grants may cover travel and accommodation and allow the purchase of basic equipment essential for the needs of such training courses.
- assistance of national microbiological facilities, e.g. culture collections (which underpin microbiology), where these run into temporary difficulties.
- any other small project to assist in technology transfer from developed countries to the areas mentioned above for which other sources of funding do not exist.

Applications to the Fund are now invited. Four copies, including full supporting documents, should be sent to the Grants Office at SGM HQ.

The closing date for applications is **11 October 2004**.

The full rules of all Society grant schemes are available on the SGM website at **www.sgm.ac.uk**. Please consult these before applying for an award. You can download the application forms for schemes where these are required. Click on the 'Grants & Funding' button for details.

Any enquiries should be made to the Grants Office, SGM, Marlborough House, Basingstoke Road, Spencers Wood, Reading RG7 1AG [Tel: +44 (0)118 988 1821; Fax: +44 (0)118 988 5656; email: grants@sgm.ac.uk].

Education Development Fund Awards

The following Public Understanding of Science grant has been made:

Dr Vyv Salisbury, University of the West of England has been awarded up to £1,000 towards the expenses of running a microbiology promotion display at the @Bristol Science Centre entitled *Lighting Up Biomedical Research*.

Education Development Fund 2004

Members are invited to apply for small grants to fund either (a) initiatives to promote the public understanding of microbiology or (b) to support developments likely to lead to an improvement in the teaching of any aspect of microbiology relevant to secondary or tertiary (including postgraduate) education in the UK. There are different application forms for the PUS awards and the teaching aids. There is no closing date for applications, which will be considered on a first come, first served basis during the calendar year.

Technician Meeting Taster Grants

These grants, which enable eligible technicians to sample an SGM meeting with expenses of up to £200 being met by the Society, are still available for the Trinity College Dublin meeting (6–9 September 2004). See SGM website for full details and an application form.

Retired Member Conference Grants

The scheme enables retired members to attend one SGM meeting per year. The grant covers en-suite accommodation and the Society Dinner. The maximum award is £250. It is hoped that the scheme will enable retired microbiologists both to keep up with their science and to share their knowledge with other members. Completed application forms must be submitted to the Grants Office before the meeting. Applications are now invited for grants to attend the Society's meeting at Trinity College Dublin, 6–9 September 2004.

Seminar Speakers Fund 2004

The Fund aims to promote talks on microbiological topics in departmental seminar programmes. Applications are invited from higher education institutions where microbiology is taught for total grants of up to £200 towards the travel, and if necessary, accommodation, expenses of up to two invited speakers. Applications will be dealt with on a first come, first served basis during the academic year. Written submissions should be sent to the Grants Office at SGM Headquarters for consideration.

The Watanabe Book Fund

Members who are permanently resident in a developing country are reminded that they may apply for funding to acquire for their libraries books, or possibly journals, relating to microbiology. These annual awards are available as a result of a generous donation from Professor T. Watanabe of Japan. The closing date for the receipt of applications, which should be made to the Grants Office at SGM Headquarters, is **11 October 2004**.

Meetings

Meetings on the web

For up-to-date information on future Society meetings and to book on-line see: **www.sgm.ac.uk**

Meetings organization

The SGM meetings programmes are organized by the committees of the special interest groups, co-ordinated by the Scientific Meetings Officer, **Professor Howard Jenkinson**. Suggestions for topics for future symposia are always welcome. See p. 104 for contact details of Group Conveners.

Administration of meetings is carried out by **Mrs Josiane Dunn** at SGM Headquarters, Marlborough House, Basingstoke Road, Spencers Wood, Reading RG7 1AG (Tel. 0118 988 1805; Fax 0118 988 5656; email meetings@sgm.ac.uk).

Offered papers and posters

Many Groups organize sessions for the presentation of short oral papers or allow intercalated papers within their symposia. Offered posters are welcome at all Society meetings.

Offered posters

Each poster should be associated either with the Plenary Session topic or with a Group. The subject content of the latter should be relevant to the remit of a Group (see website for details); it does not have to relate to the topic of the Group Symposium taking place at a particular meeting. General Offered Posters will not be accepted.

Abstracts

Titles and abstracts for all presentations are required in a standard format and should be submitted through the SGM website. Deadlines for submissions are published in *Microbiology Today* and on the web. For further information contact the Events Administrator.

Bath meeting

29 March– 2 April 2004

Microbe–Vector Interactions in Vector-borne Diseases – *Symposium Volume 63*

This is now available from CUP at a special discount price for members. A review of the book appears on p. 96 and an order form is included in this issue.

Abstracts book

The full text of the abstracts book is now available as a PDF file on the SGM website.

Future Meetings

AUTUMN 2004 – 155th Meeting

Trinity College, Dublin, 6–9 September 2004

The City of Dublin promises to be an exciting venue for the autumn meeting, which is the first the SGM has held outside the UK for several years. A packed programme of symposia and workshops has been planned, but the format of the meeting will be different in many ways from usual.

● ACCOMMODATION

The scientific sessions will take place in Trinity College, but delegates will be responsible for booking their own overnight accommodation. Arrangements have been made with Total Stay – The Hotel Shop who are offering bed and breakfast in hotels at prices to suit all pockets. Bookings should be made directly with the agency by telephone (Tel. 0870 0112 292) or online (www.totalstay.com).

● MEALS

No meals will be available at Trinity College. There is a huge variety of cafes, bars, restaurants and pubs nearby where delegates can buy lunch and dinner.

● REGISTRATION FEES

£25 per day will be payable by SGM members for this meeting. Non-member registration fees are £70 per day. These include refreshments, the abstracts book, all conference literature and administration. Student Members, Retired Members and Honorary Members are exempt from registration fees.

● POSTGRADUATE CONFERENCE GRANTS

These will be available, subject to the usual conditions. A flat rate will be paid for accommodation of £30 per night plus daily subsistence of £10. For full details, a form and allowances for travel see www.sgm.ac.uk/grants/pg.cfm

● SOCIAL EVENTS

Irish Night

Instead of a formal Society Dinner, there will be an evening of unlimited Irish food, drink (including Guinness, of course), music, dancing and other traditional entertainments.

Trinity College

There are many attractions within the College, including the Old Library, Book of Kells and the Dublin Experience exhibition. Tickets will be available at concessionary prices for conference delegates.

Old Jameson Distillery

Tour the famous Irish whiskey distillery, followed by drinks and a finger buffet.

● Plenary: Alternative anti-microbial therapies

Organizers: I.R. Henderson, P.M. Hawkey, K. Bamford, J.N. Fletcher, T.J. Foster & H.F. Jenkinson

● Speakers

D.J. PAYNE (USA)
Novel targets for future development of antibacterial agents

M.B. SCHMID (Canada)
Structural proteomics for new antimicrobials

A. SNELLING (Bradford) & P.M. HAWKEY (Birmingham)
E. coli *and probiotics as antibacterials*

P.A. GULIG (USA)
Phage therapy of local or systemic disease

I. OFEK (Israel)
Inhibitors of microbial adhesion to host tissues

A. BELL (TCD, Ireland)
New approaches to antimalarial drugs

C.G. KELLY (KCL, London)
Peptide inhibitors of oral bacterial adhesion

J.M. PATTI (USA)
Antibody inhibitors for staphylococci

M.A. SCHMIDT (Germany)
Auto transporters as delivery vehicles

D.H. PERSING (USA)
Lipid A mimetics as adjuvants and immunomodulators

V.A. FISCHETTI (USA)
Lysins for streptococci and pneumococci

P.B. ERNST (USA)
Vaccines that alter the gastric immune response

R.W. HANCOCK (Canada)
Host defence peptides

C. SVANBORG (Sweden)
Receptor depletion in antimicrobial therapy

J.P. NATARO (USA)
Entero-aggregative E. coli

● Other symposia

● Lactic acid bacteria

8–9 September

Irish Branch/ Food & Beverages/ Systematics & Evolution Groups

Organizers: R. Rastall (r.a.rastall@reading.ac.uk), M.A. Collins (m.collins@qub.ac.uk), G. Saddler (gerry.saddler@sasa.gsi.gov.uk), F.G. Priest (f.g.priest@hw.ac.uk) & C. O'Reilly (coreilly@wit.ie)

● Secreted effector molecules

6–7 September

Cells & Cell Surfaces Group

Organizers: B. Kenny (b.kenny@bris.ac.uk) & M. Stevens (Mark-P.Stevens@bbsrc.ac.uk)

● E-sy learning

8 September

Education & Training Group

Organizers: J. Parry (j.parry@lancaster.ac.uk) & S. Assinder (s.assinder@bangor.ac.uk)

● Functional genes and functional genomics in the environment

8–9 September

Environmental Microbiology Group

Organizers: J.D. Porter (j.d.porter@ex.ac.uk) & D.C. Naseby (d.c.naseby@herts.ac.uk)

- Microbial epigenetics

8–9 September

Eukaryotic Microbiology Group/ Genetics Society

Organizers: A.S.H. Goldman (a.goldman@shef.ac.uk) & M.F. Tuite (m.f.tuite@ukc.ac.uk)

- Gram-positive cell factories

7 September

Fermentation & Bioprocessing Group

Organizers: P.A. Hoskisson (paul.hoskisson@bbsrc.ac.uk) & G. Hobbs (g.hobbs@livjm.ac.uk)

- Zoonotic infections

8 September

Microbial Infection Group

Organizer: C. Winstanley (c.winstanley@liv.ac.uk)

- Molecular chaperones and protein folding

7 September

Physiology, Biochemistry & Bioprocessing Group

Organizer: W. Ashraf (w.ashraf@bradford.ac.uk)

● Young Microbiologist of the Year Competition

7 September

This competition is sponsored by the Society to encourage excellence in scientific communication by young microbiologists. Group Committees have now judged recent oral or poster presentations by members who are postgraduate students or postdocs who have gained their PhD in the past 2 years. The finalists from each Group go forward to compete for prizes at a special session of short oral presentations on their research. The three best entries win cash prizes: **1st**, £500; **2nd**, £200; **3rd**, £100. All finalists receive a year's free SGM membership.

● Abstracts

Deadline for receipt of titles and abstracts for offered presentations: **7 May 2004**.

● Registration

A booking form is available on p. 107 or register on-line at **www.sgm.ac.uk/meetings**

Deadline for early registration: **Friday 6 August**. Thereafter a late booking charge will be incurred.

SPRING 2005 – 156th Meeting

Heriot-Watt University, 4–7 April 2005

● Plenary: Molecular pathogenesis of virus infections

● Other symposia and workshops

- Molecular typing and epidemiology

Clinical Microbiology/ Systematics & Evolution Groups

- Antibiotic resistance

Clinical Microbiology Group/ BSAC

- Virology: is it practical?

Education & Training Group

- Microbe-pollutant interactions

Environmental Microbiology Group

- Analysis of fermentation processes

Fermentation & Bioprocessing Group/ IChemE

- Evolving bacteria and emerging foodborne disease

Food & Beverages Group/ IFST

- Non-mammalian models of infection

Microbial Infection Group

- Bacteriophages

Physiology, Biochemistry & Molecular Genetics/ Cells & Cell Surfaces/ Microbial Infection Groups

- Cell tropisms and host range

Virus Group

- Workshops

Virus Group

Irish Branch

Microarray workshop

Dublin City University
3–4 June 2004

Organizers: Nick Dorrell, Jason Hinds, Catherine O'Reilly & Michael O'Connell

Environmental genomics

University College Cork
Spring 2005

Organizer: Julian Marchesi

For details of Irish Branch activities contact the Convener, Catherine O'Reilly (coreilly@wit.ie)

Other News & Events

● Bioinformatics Workshops

Following the success of the workshops held jointly by the SGM and The Sanger Centre in 2003 Council is sponsoring further events this year. See p. 87 for details and a booking form.

● European Virology 2004

5–9 September 2004
Campus Universidad Complutense, Madrid

The programme will be of interest to both basic and clinical virologists.

www.madridvirology2004.com

● IUMS Congresses

Microbes in a Changing World

Joint Meeting of the three Divisions of the International Union of Microbiological Societies

23–28 July 2005
San Francisco, CA, USA

Hosted by the American Society for Microbiology

Abstract deadline:	11 February 2005
Early registration:	13 May 2005
Registration & housing deadline:	1 June 2005

www.iums2005.org

SGM travel grants will be available. Details will be posted on the SGM website soon: **www.sgm.ac.uk/grants**

Gradline

Gradline Editor Jane Westwell focuses on careers in this issue, offering advice from UK Next Wave's Careers Doctor, Sara Shinton and profiling a job in science communication.

If you have any stories or news for publication in Gradline, or if you would like to see any topics featured, contact Jane Westwell (**j.westwell@sgm.ac.uk**).

Career development workshop

Your PhD and beyond

University of Bath, 1 April 2004

Postgrads and postdocs attending the recent SGM meeting at Bath were able to hone their personal skills by attending an evening workshop organized by Jane Westwell. Council Member Hilary Lappin-Scott chaired the session, a highly interactive one led by professional career consultants Andrew Bottomley and Sara Shinton. The first talk was on presentation skills and included 'volunteers' from the audience demonstrating speakers' strengths and weaknesses. This was followed by a session on CV writing (see below) and concluded with some career planning tips. At the end John Peberdy enthused the audience with a brief run-down on the Biotechnology YES competition, which provides a good deal of training in personal development for entrants. After all the hard work it was time for a buffet supper, a glass or two of wine and the chance to browse around displays by recruiters SRG, SGM, UKGRAD, Biotechnology YES and Science's Next Wave. SGM is grateful for their support.

Career Planning: Writing Your CV

Sara Shinton

My first visit to an SGM Meeting was extremely enjoyable and I'd like to start by thanking everyone who came to the Career Development workshop or the CV clinic I ran. For those of you who were unable to attend, I hope that by summarizing some key points and resources which I regularly refer to, I can help you begin your own career planning as well.

I must also thank Science's Next Wave for sponsoring my attendance. As Next Wave's 'CareerDoctor' I write a monthly column addressing individual career queries and concerns, so if you don't find the advice you are looking for in this article, why not email me (careerdoctor@science-int.co.uk) and I'll try to address it in future?

During the SGM workshop I presented the golden rules for CV writing (you can also take a look at the slides on my website www.shintonconsulting.com/sara/downloads.html until 1 August):

First impressions

Whenever I look at a CV, I hope I'll be able to pick up from it what kind of work its author is looking for. The way in which academic research is described often gives me the greatest clue. If the description is very technical and makes no attempt to engage the non-specialist, I'll assume that this CV is aimed at relevant research posts. If there is little evidence of generic or transferable skills or additional interests, simply a list of conferences, publications and technical skills, I'll then assume this post is in the academic sector, where the main emphasis is on research expertise and impact. If you're planning to leave academia, is your CV painting the right picture?

Visual impact

Although my years as a bench scientist are long gone, one of the many research skills that I continue to utilize is giving information visual impact – something I learnt when producing posters for conferences. CVs are not so different from posters – they need clear navigation, easy-to-read fonts and a balance between information and 'white space' so as not to overwhelm the reader. The jury is out on whether to include photographs, but they can be very useful in speculative applications if you have previously met the person receiving the CV. Make sure it is appropriate – not a holiday snap or one obviously taken in your preferred hostelry.

Balancing your skills

Try to relate the amount of space you give to each element on your CV to its relevance to the job. There's no need to list every single undergraduate module or have a list of every scientific technique you've ever used – focus on the skills and experience that the employer is looking for.

Presenting your research

A standard rule is that CVs should be 2 pages long, although I frequently tell researchers to bend this rule a little by using an appendix to describe their work in greater length. This means that anyone who is not a specialist can focus on the CV, where they will find details of qualifications, skills and experience. Fellow researchers can focus on the appendix, which can include full details of publications, conferences, any funding awarded and an outline of your research strategies and aims for future work. You can also pull together several research projects into a coherent story, rather than breaking them up in a career history. Don't be afraid to use schematics or diagrams in an appendix if this is the most effective way to communicate your science, but don't get carried away as your appendix will ideally only be a single page.

Even with an appendix, the main body of the CV should still include a brief summary of your research, not just the title. I like to suggest researchers focus on aims and achievements and have written example CVs (see www.grad.ac.uk/2_2_5_2.jsp).

Attention to detail

Anyone who regularly looks at CVs will urge you to strive for perfection in the presentation of your application. Spelling mistakes and grammatical errors are likely to eliminate your CV from the shortlist. Covering letters referring to the wrong company or position are also common, having been adapted from applications for different jobs. Also ensure that you include dates, names of employers and general locations (not full addresses) when describing your background. It can be

Postgrads and postdocs – Still chance to be entrepreneurial

The Biotechnology YES and BioScience YES Competitions for 2004 have now been launched so now is the time get organized and submit your team. Visit **www.biotechnologyyes.co.uk** or, if you are working in a Yorkshire University **www.bioscience.co.uk** and register NOW.

difficult to spot obvious mistakes in your own writing, which brings me neatly to my final point!

Feedback

All of you have access to expert advice. I would urge you to make the most of your university careers service. Try to talk to an adviser who knows something about scientific or research careers, but if they can't answer very specific questions, remember that the SGM and Next Wave websites carry a wealth of relevant information.

Sara Shinton is a freelance careers consultant and worked with UK GRAD to develop the careers-focused GRADschool.

http://nextwave.sciencemag.org/uk

http://www.shintonconsulting.com/

Careers help from SGM

The SGM's dedicated careers website is at www. biocareers.org.uk and we can also answer individual queries (within reason!) if you email careers@sgm. ac.uk. A range of job profiles is on the Biocareers site. If you would like to see your career path in print or on-screen, then let us know.

Don't miss the postgrad event at next year's spring meeting at Heriot-Watt University. It will try to help you to make a success of your PhD with sessions on *Managing Your Supervisor*, *Writing Up* and *Surviving Your Viva*. As usual the workshop will be followed by drinks and a buffet. Keep an eye on the website or these pages for details.

A job in... Science Communication

Profile

Name Emma Southern

Age 30

Present Occupation
Deputy, Corporate Affairs: Babraham Institute, Cambridge

Previous Employment
Nov 00–July 03: *Communications Manager, Astex Technology, Cambridge*
Oct 99–Oct 00: *R&D Scientist, IDEXX Genera, Newmarket*
May 96–Sep 96: *Microbiologist, Anglian Water, Norwich*
Oct 95–Mar 96: *Teacher of English, Moonil Language School, Seoul*

Education
PhD, John Innes Centre, *The role of sigma54 region II in transcriptional regulation*
Certificate in Teaching English as a Foreign Language, Bell Language School, Norwich
BSc, University of East Anglia, *Biological Sciences*

Q *What prompted your move into the Biotech sector after your PhD?*

I didn't feel my strengths lay in academic research. I wasn't completely sure that research in the commercial world would suit me either; however, my first job offered more than benchwork alone. It was also in an ideal geographical location for me at the time. In the end, the job was a 'stepping-stone' into my communications role at Astex. To be honest, I didn't think to look for a science communication job in an academic environment immediately after my PhD – at that time, I hadn't really decided this was the career for me.

Q *How did you find the transition from lab-based to administrative work?*

Thankfully, I found it relatively easy. My first job (as an R&D Scientist) was practical science, but was mainly computer-based. It was a small company, so there were far fewer people around, and initially I missed the busy lab environment and 'hands-on' aspect of my previous lab work. My next role was wholly office-based. But I was working on a range of different projects, and with a wide variety of people (senior management, graphic designers, lab scientists, public-relations consultants), so I was never in one place – physically or mentally – for very long! I had always enjoyed the 'administrative' side of my PhD – reading papers, writing reports and presentations, even writing my thesis (!) – so I was content to continue this type of work.

Q *What advice can you offer people looking for a similar career?*

Science communication is a popular area of work, so competition for certain jobs can be fierce. But the skills you have are applicable in a number of different environments – public relations for a scientific company, an agency or an academic institute, teaching, medical writing, science demonstrating at museums, science journalism or editing, working with schools, presenting to the public – so it's worth keeping an open mind about where you want to work. Try a few things out first: helping with open days, visiting schools, writing for an in-house publication, for example. You could opt to study for a qualification in science communication – a few places in the UK offer short courses or Masters' degrees. These may help you to refine your skills, but if you already have a sound science background and an aptitude in communicating science to a range of audiences, I think the best option is to put your skills into practice whenever you can.

Q *Why did you move to the Babraham?*

At Astex I learned all about corporate communication and gained a great deal of experience. Obviously Astex, as a private biotech company, has specific audiences – its investors, potential collaborators and other biotechs, for example. After a while, I decided that I would like the opportunity to communicate science to different audiences, including the public. Hence my move to the Babraham Institute, an educational charity carrying out scientific research to inform the biomedical and pharmaceutical sectors. Audiences include the local community, funding bodies and other research establishments. Interaction with schools is a significant part of the communications programme.

Q What does your current job involve?

I act as a press officer, helping to publicize the scientific achievements of the Institute, and am reponsible for the school liaison programme, in which we link scientists with local schools to aid science teaching in the classroom. I also have the chance to visit schools myself. The design and maintenance of the Institute's internal and external websites, and also the production of printed publications are under my care. I also liaise with the local community, to keep them informed about developments at the Institute. Additionally, I have a 'corporate communciations' role with Babraham Bioscience Technologies Ltd (the wholly-owned trading subsidiary of the Institute) involving similar press and publicity activites. And then anything else that falls under the remit of the Corporate Affairs group – I enjoy the variety!

Further information

- The Babraham Institute (www.babraham.bbsrc.ac.uk)
- STEMPRA (www.stempra.org.uk) offers practical advice for science communicators and a links page
- The Association of British Science Writers website (www.absw.org.uk) lists science communication courses, useful links and includes the downloadable document *So you want to be a science writer?*
- SGM offers small grants to support members planning science communication and outreach projects. Further information and application forms are available from the SGM Grants web pages www.sgm.ac.uk/grants/dtf.cfm

Antimicrobial update

Dariel Burdass

Keep up-to-date with what's happening in microbiology education. Schools Membership costs only £10 a year. For this, a named teacher representative will receive *Microbiology Today* each quarter, 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

Education website: www.microbiologyonline.org.uk

Once thought to be conquered, infectious diseases continue to tax all the ingenuity of microbiologists who strive to keep ahead of the mutating microbes in the quest for effective treatments.

SGM Education Projects Administrator Dariel Burdass gives an overview of the current situation with antibiotics and other antimicrobials. A more detailed version of this article will shortly appear as a 'Factfile' for distribution widely to schools.

What are antimicrobial agents?

Antimicrobial agents are chemicals that kill or inhibit the growth of micro-organisms and are used to treat microbial infections. Some are produced naturally by microbes, but many are now synthetic.

Antibacterials (antibiotics)

Antibiotics are secondary metabolic products of both soil bacteria and fungi. However, the term antibiotic now refers to both synthetic and naturally occurring compounds and is most commonly associated with drugs used to treat bacterial infections.

Alexander Fleming discovered penicillin, the first antibiotic, in 1928. He isolated it from the mould *Penicillium notatum* and found it prevented the growth of bacteria even when diluted up to 800 times. Penicillin was not available for commercial use until Florey and Chain purified it in 1940.

The 1940s saw the mass production of penicillin and this led to an enormous reduction in illness and death from bacterial disease. The result was an explosion of research in this field and many new classes of antibiotics were discovered. Antibiotics were seen as 'magic bullets' due to their ability to cure the patient by targeting the infective agent precisely without affecting the host. This led the US Surgeon General William H. Stewart to tell congress in 1969 '*the time has come to close the book on infectious disease*'.

How do they work?

Antibacterials exploit the difference between the prokaryotic bacterial cell and the host's eukaryotic cell. They work by being either bacteriostatic, preventing cells from multiplying so that the bacterial population remains static, allowing the host's defence mechanism to fight the infection, or by killing the bacteria (bactericidal).

This is achieved by interfering with one or more of the following processes:

- Cell wall synthesis and integrity, e.g. penicillin
- Cell membrane function and structure, e.g. polymixin
- Protein synthesis, e.g. tetracycline
- Nucleic acid synthesis, e.g. rifampicin.

Antibiotics are classified either as:

- broad spectrum, acting on both Gram-negative and Gram-positive bacteria, or
- narrow spectrum, acting on only a single group of bacteria.

The emergence of drug-resistant bacteria

Micro-organisms are termed drug-resistant when they are no longer inhibited by an antimicrobial to which they were previously sensitive.

In the late 1940s, only 4 years after mass treatment with penicillin had been introduced, a strain of the bacterium *Staphylococcus aureus* was shown to be resistant to this drug. The emergence and spread of antibacterial-resistant micro-organisms has continued to grow due to both the over use and misuse of antibiotics.

How has this happened?

Many factors have contributed to this rise in resistance and include the following:

- Pressure on GPs to prescribe. The House of Lords Select Committee on Science and Technology 1999 reported '*Patients' expectations and doctors' perceptions of patient expectations may result in doctors prescribing antibiotics to keep patients happy, even if they are not needed*'.
- Antibiotics are commonly prescribed for respiratory infections when the vast majority of these are caused by viruses not bacteria.
- Most patients are prescribed antibiotics without the doctor knowing the cause of the infection.
- Poor patient compliance, e.g. failing to take the full course of antibiotics prescribed. This has been a particular problem when treating TB. Treatment is long (6–9 months), but patients often stop taking their antibiotics after 1 month when they start to feel better.
- Heavy use of antibiotics in hospitals. ITCUs, burns units and specialist surgical care units have the highest usage of antimicrobials and these areas also have the highest occurrence of antimicrobial-resistant bacteria. Frequent contact between medical staff and patients increases the chance of cross infection. It has been reported that up to 75% of hospital staff carry methicillin-resistant *Staphylococcus aureus* (MRSA). Colonization with these resistant bacteria can occur even in patients not being treated with antibiotics.
- In many developing and even some western countries antibiotics can be purchased over the counter in pharmacies and general stores, leading to inappropriate and/or over use.
- Poor quality antibiotics in some countries.
- Use of antibiotics in animals for growth promotion and prophylaxis, which can lead to them entering the environment.

Why do micro-organisms produce antimicrobials?

In the environment antimicrobials have the following roles:

- They improve the survival of the producer in competition with other bacteria, fungi, amoebae, plants, insects and large animals.
- They act as metal-transporting agents.
- They act as agents of symbiosis between the microbe and other organisms such as plants, nematodes and insects. For example, in the case of a symbiotic relationship between fungi and plant roots, the fungi produce antibiotics that protect the plant against pathogenic fungi or bacteria, and the plant provides the fungi with nutrients.
- They can stimulate spore formation and inhibit or stimulate germination.

TOP LEFT:
Antibiotic droplet exuding from a mycelial colony of *Streptomyces coelicolor*.
COURTESY MERVYN BIBB, JOHN INNES CENTRE, NORWICH

Survival of the fittest

When an antibiotic is first used the percentage of resistant strains is less than 1 %. After 8–12 years, if the antibiotic is in regular use, the level of resistance increases dramatically.

How antibiotic resistance spreads

Treating a patient with antibiotics causes the microbes to adapt or die; this is known as 'selective pressure'.

If a strain of a bacterial species acquires resistance to an antibiotic, it will survive the treatment. As the bacterial cell with acquired resistance multiplies, this resistance is passed on to its offspring. In ideal conditions some bacterial cells can divide every 20 minutes; this means that after only 8 hours in excess of 16 million bacterial cells carrying resistance to that antibiotic could exist.

The human body is home to a normal flora which colonizes surfaces and reduces the availability of nutrients and space to pathogenic bacteria. Therefore, in a healthy person it is difficult for these pathogens to gain a hold and exist in large numbers. When a person takes a broad spectrum antibiotic, e.g. ampicillin, the antibiotic does not discriminate between the pathogens and the beneficial normal bacterial flora of the body so that both will be killed. A reduction in the numbers of resident flora will give any bacterial pathogen resistant to the antibiotic an increased competitive advantage. It may then multiply, predominate and cause disease.

How are resistance genes spread?

Antibiotic resistance can either be inherent or acquired.

1. Inherent resistance. Some bacteria are naturally resistant to some antibiotics due to their physiological characteristics.
2. Acquired resistance. This occurs when a bacterium that was originally sensitive to an antibiotic develops resistance. This can be due to:
   - Random chromosomal mutation. Mutation is a spontaneous event and occurs regardless of whether an antibiotic is present or not. A mutation in chromosomal DNA is usually only effective against a single type of antibiotic. Drug-resistant TB arises this way.
   - Transfer of extrachromosomal DNA from a resistant species to a sensitive one. Transferable resistance was first identified in 1959 when resistance genes found in *Shigella* transferred to *E. coli* via plasmids. Resistance (R) plasmids can transfer multiple resistance genes. R plasmids can be transferred by conjugation (bacteria have to be in direct contact to exchange genetic material) and transduction (the transfer of DNA via a bacteriophage).
   - Resistance genes can also be transferred from one plasmid to another plasmid or chromosome. The mobile genetic element is known as a 'jumping gene' as it is able to insert itself anywhere along the genome.

With the emergence of antibiotic-resistant bacteria increasing at a faster rate than the discovery of new drugs the WHO, through its antimicrobial resistance monitoring (ARM) activities, and in conjunction with other bodies, is working to develop and implement a global strategy for the control of antimicrobial resistance.

Reversing antibiotic resistance

In 1997 Professor Altman and his team at Yale University published a paper in *PNAS* showing how they had developed a method for reversing drug resistance in bacteria using plasmids containing synthetic gene codes to inhibit bacterial production of proteins that confer antibiotic resistance. It is possible that in the future this technique could be a viable alternative to the present approach of developing new antibiotics.

Discovery of new antibiotics using genomics

The entire genomic sequences of many bacterial pathogens are now known. This allows scientists to identify new drug targets and should lead to improvements in the design and development of future antibiotics (see the articles by David Payne p. 55 and David Hopwood p. 64 in this issue).

Antifungals

Fungal cells and human cells are both eukaryotic and share many structures and metabolic pathways. A successful antifungal agent must have greater activity against the fungal cell than the human cell, i.e. it must not be toxic to the human cell. This is very difficult to achieve. Serious fungal infections, which are associated with immunosuppressed conditions such as AIDS and transplantation, have grown in clinical importance in recent years as has the number of affected patients in this state. Also, environmental fungi that are not normally regarded as pathogens are infecting such patients and causing disease, e.g. *Fusarium*, a common soil and plant pathogen.

Some common fungal ailments can be treated with over-the-counter drugs. For example, fluconazole is used against superficial *Candida* infections.

Antifungal resistance is less of a problem than antibacterial resistance; however, certain strains of *Candida* species that are resistant to azoles have been isolated. This is worrying because patients with suppressed immune systems are at particular risk of developing *Candida* infections.

An increasing amount of research is now being conducted to identify new targets that are unique to a specific fungus. Once again, genome-based approaches are being used.

Antivirals

For most viral infections there is no specific treatment. It is difficult to develop antivirals, as it is hard to find a drug that successfully inhibits virus replication without affecting the host cell. This is a direct result of virus replication taking over the biochemical machinery of the host cell. However, rapid progress has been made in recent years and now over 30 antiviral drugs are available, as described on p. 58 in this issue. Acyclovir is probably the best known antiviral, sold without prescription to combat cold sores caused by the herpes simplex virus.

Resistance to antivirals is not common but does occur.

The advent of AIDS has stimulated an intensive research programme into new antivirals.

Antibiotics cannot be used to treat viral infections, although, they are sometimes given to treat secondary bacterial infections which can occur after the immune system has been weakened fighting a viral infection.

Further sources of information

Altman, S. & others (1997). Phenotypic conversion of drug-resistant bacteria to drug-sensitive. *Proc Natl Acad Sci USA* 94, 8468–8472.

Mims, C.D. & others (1998). *Medical Microbiology*, 2nd edn. Mosby. ISBN: 0 7234 2781 X.

Myint, S.H. & others (1999). *Medical Microbiology Made Memorable*. Churchill Livingstone. ISBN: 0 4430 6135 1.

Wilson, J.F. (2002). Renewing the fight against bacteria. *The Scientist* 16, 22–23.

Various UK parliamentary reports. www.publications.parliament.uk (search for 'antibiotics').

World Health Organisation www.who.int/inf-fs/en/fact194.html

Centers for Disease Control (USA) www.cdc.gov (search for 'antibiotics').

SGM Micro-Encyclopedia

The articles in *Microbiology Today* are made available on the SGM website as downloadable PDF files. These have all been classified by subject and make a great resource for teaching. Go to the SGM home page **www.sgm.ac.uk** and click on 'Micro-Encyclopedia'. Follow the links on the left hand side to search for articles on a given topic. For example, for features on antibiotics click on 'Human' under the 'Diseases and Treatment' section where the following can be found:

The enemy within – hospital-acquired antibiotic-resistant bacteria Peter Hawkey (Feb 2001).

New drugs for the super bugs Ian Chopra (Feb 2000).

Microbiology in the News

For the latest microbiology as reported in the media click on 'News Desk' which can also be found via the SGM website. This is arranged chronologically and summarizes the topics as they appear in the broadsheet newspapers, *BBC Online* and other publications every day. This is also a useful resource for finding background information on microbiological issues.

School Member survey

Recently a questionnaire was circulated to all School Members to evaluate current and future SGM educational resources and initiatives. 7 % kindly responded.

Profile of respondents

Of those that responded, 74 % teach microbiology at key stage 3, 87 % at key stage 4 and 96 % post-16 with an average of 3 hours, 6 hours and 15 hours, respectively being spent on practical microbiology teaching at each of the key stages. The majority use the AQA specifications at both GCSE and A level with 61 % teaching the optional A2 module in biotechnology/microbiology.

Current SGM resources

It was pleasing to note that 91 % find the current microbiology resources either moderately or highly relevant to the curriculum. When asked if the resources are used to support microbiology teaching, over 74 % said they use the posters, 83 % the practical microbiology book and 75 % said they use all the factfiles (except *Biofilms*).

Future resources

Over 86 % thought that the future planned resources were relevant to the specifications. However, less than 50 % thought that they would use either the algae or tea tree practicals in their teaching sessions. AIDS and the body's defence system against microbes were the two most popular of the proposed fact files with 100 % thinking they were relevant to the specifications and 75 % indicating they would use these in their future teaching.

The most popular format for teaching resources continues to be paper with PowerPoint second, video third and web-based fourth.

This information will be taken into account when planning new resources, along with any additional comments that were made.

SGM Summer School

12–16 July 2004, University of Leeds

Places are available for this residential event which aims to update post-16 biology teachers on microbiology topics in the curriculum. The specification-led programme is now available on the SGM's dedicated microbiology education website **www.microbiologyonline.org.uk**, where you can also download a booking form. As well as lectures, workshops and hands-on practicals, there are outings and social events, plus the opportunity to meet top microbiologists.

The lectures are organized into themes:

- Molecular Microbiology
  Post genomics (Kenny McDowell)
  Microbial immunology (Eileen Ingham)
- Biotechnology
  Drug development (Ian Chopra)
  Exploitation of enzymes (Bob Rastall)
  Fermentation (Geoff Robson)
- Infectious Disease
  Bacterial disease (John Heritage)
  TB (Debbie Gasgoyne)
  Viral diseases – hepatitis and HIV (Dick Killington)
  Fungal diseases (Dick Hobson)
  Malaria (Glen MacConkey)
- Science Education
  The new Salters–Nuffield Advanced Biology and the National Network of Science Learning Centres (Anne Scott)
  Improving teaching and learning in post-16 biology (Michael Kalvis, DfES)

There will also be an emphasis on science communication, with a workshop led by eminent science writer Bernard Dixon and a poster competition.

Three afternoons will be devoted to practicals, to include measuring fungal growth; testing antimicrobial sensitivity; use of the microscope and Gram staining; fungal identification; datalogging; DNA fingerprinting; pGLO transformation.

The course fee is only £130, which covers all accommodation, meals, course materials and outings. Teachers from SGM member schools pay only £100.

Email **education@sgm.ac.uk** if you have any queries.

Dariel Burdass, SGM Education Projects Administrator

Microbiology Awareness Campaign Scotland

SGM Council, through its Professional Affairs Officer Geoffrey Schild and with the help of many members, has initiated a campaign to raise the awareness of microbiology to UK politicians and their supporting staff. It also wishes to alert them to the existence of the Society as a source of information and to stress the importance of professional microbiologists. The Campaign will be moving around the country, but where better to launch it than in Scotland where microbiology has a high profile?

Microbiology in Scotland

Janet Hurst

Many people receive an education in microbiology in Scottish schools, colleges and higher education institutions. Compared with the rest of the UK, a high proportion of medical practitioners and vets are trained there. Microbiological work of all kinds is carried out in a wide range of excellent research institutes, agencies, university departments and hospitals. The commercial biotechnology sector, much of which is underpinned by microbiology, is successful and provides considerable employment. The EU recognizes Scotland as a dedicated Biotechnology Cluster.

Scottish politicians and civil servants often have to make important policy decisions on microbiological issues. The health of people, animals and plants, agriculture, the environment, food and drink production (think whisky!) all fall within their remit. Yet how many MSPs are scientists, let alone microbiologists? The answer to the first question is in single figures and to the second, none! With 600+ members in Scotland, the SGM is well-placed to provide the Scottish Parliament with expert guidance.

The event

On 4 March SGM hosted an event at 'The Hub' on Edinburgh's Royal Mile, conveniently located just across the road from the Scottish Parliament. All Scottish MPs and senior staff from relevant departments of the Scottish Executive were invited to meet a wide range of microbiologists over lunch. The programme included some very brief talks and delegates were also able to browse around the 20 displays which showed the huge breadth of microbiology practised by Scottish organizations.

107 people attended the event, including 14 MSPs – a very good turnout considering the busy session that day in the Scottish Parliament. Labour MSP Dr Elaine Murray, a former deputy minister who *is* a scientist, gave the introduction and welcomed the SGM to Scotland. She was followed by SGM President Hugh Pennington, a well known figure in Scottish medical and food safety circles, who described the Society's activities before talking on human and animal microbiology issues in Scotland (see p. 89). David Onions, Professor of Veterinary Virology at the University of Glasgow and founder of Q-One Biotech, now part of the Invitrogen/BioReliance group, explained why microbiology means business. The diverse aspects of aquatic microbiology were then explored by Brian Austin, Professor of Microbiology at Heriot-Watt University (see p. 90).

The politician's view

The proceedings were wrapped up by Tom McCabe, MSP, Deputy Minister for Health and Community Care, who took time out of a hectic schedule to attend. In contrast to the previous contributions, Tom talked about science from a political angle. He emphasized how delighted he was to support the SGM campaign and how he understood the need for microbiologists. He recognized the important part microbiology played in Scottish life, from the earliest times through to its current role in the Scottish economy, but not forgetting the challenges posed today by microbial disease. He then set out some of the Scottish Executive's approaches to life science issues and noted that in the last spending review the Executive had provided a 20 % increase in funding in real terms for university research. Scotland's first ever integrated Science Strategy was published in 2001. *'We intend reporting on progress and updating the Strategy this*

BELOW:
Inside spread from the SGM Microbiology Awareness Campaign Scotland leaflet.

OPPOSITE PAGE TOP:
Delegates at the SGM Microbiology Awareness Campaign Scotland event held in Edinburgh on 4 March.

LEFT:
Hugh Pennington with Elaine Murray MSP (top) and Tom McCabe MSP, Deputy Minister for Health and Community Care (bottom).

PHOTOS RON FRASER, SGM

spring.' This will be in the light of the Scottish Science Advisory Committee's recent report *Science Matters* which identifies broad subject areas, including biological sciences, biotechnology, medical and veterinary sciences, that are of key importance in the context of a Scottish Science Strategy. Tom was glad to hear that the SGM has made a connection with the Committee and encouraged the Society to develop these links as the Committee moves into a new important phase of work to recommend the priorities in the medium and long term for science expenditure.

In conclusion he said, '*It is fair to say that while society at large may be unaware of the impact the microbiologist has on their quality of life, those of us who have attended events such as today's are afforded the opportunity to become much better informed. May I therefore compliment the Society on today's seminar and more generally on the extremely valuable contribution it makes to promoting microbiology through the range of activities it sponsors, not least the international conferences it regularly holds in Scotland.*'

This endorsement brought a most successful event to a close.

Microbiological challenges: the role of the SGM

Hugh Pennington

To a microbiologist, justifying our subject is the easiest thing in the world. We know about its birth to death relevance to health and well-being, our food and our industries, to take some obvious examples. But how well-informed are our parliamentary representatives? The main purpose of the Microbiology Awareness Campaign Scotland was to do our best to bring them up to speed.

I opened by explaining the functions and aspirations of the SGM, not just as Europe's largest microbiology society, but as a truly joined-up organization with members, activities and journals covering all shades and specialisms microbiological, and as a one-stop-shop for advice.

Obeisance (fully justified by any criteria) was then made to the outstanding contributions made by scientists in Scotland. Even in Edinburgh it is permissible to say that Joseph Lister's microbiologically based revolutionary surgical innovations in the 1860s and 1870s were worked out in Glasgow! These kinds of contributions continue, of course, and I pointed out that Scotland continues to punch above its weight in microbiological science both in research output and as a net exporter of microbiologists; the only thing preventing it doing even better are funding constraints.

The rest of my presentation addressed current microbiological challenges, ones of the kind that legislators understand. Bat rabies killed a wildlife worker in Tayside a couple of years ago, the first indigenous UK transmission for almost a century and an opening example of the theme running through my talk, the fact that microbes present a unique challenge to policymakers and the scientists advising them because they evolve in real time.

The next example was *E.coli* O157. The outbreaks at Wishaw in 1996 and at the New Deer Millennium Scout Camp in 2000 were described to make the points that this novel pathogen has had more impact on human health in Scotland than in any other country, that it continues to be commoner there than anywhere else, and even if the incidence of human infections has fallen (maybe due to control measures) we still do not understand why Scotland has been singled out.

Scotland escaped SARS. I pointed out that this was good luck; unlike guests from Singapore, Hong Kong, Vietnam and Canada no Scots had been staying at the Hotel Metropole in Hong Kong during the residence there of 'Patient A' from Guandong who was suffering from the disease.

Bioterrorism was considered and put into perspective by my final pathogen, influenza, with reminders of 1918, with at least 20 million deaths, and an illustration of President Ford being vaccinated on 14 October 1976 on television during the swine 'flu crisis in the United States which led to the unnecessary vaccinations of 40 million Americans, a loss of faith in public health officialdom, and which contributed to his defeat in the presidential election.

I concluded with Sam Goldwyn's quote, which summarizes the problem faced by policymakers when coping with evolutionary uncertainty; '*making predictions is difficult, particularly about the future.*'

SGM affiliates to Scottish Parliament Science Information Service (SPSIS)

The service has been set up to ensure that all MSPs have access to reliable, rapid and impartial information on science-, engineering- and technology-related issues to assist with parliamentary activities. The service is provided through a network of topic co-ordinators who are established in their field and will provide expert information that MSPs can use to make their own judgements. Established by the Royal Society of Edinburgh, Royal Society of Chemistry and the Scottish Parliament Information Centre (SPICe), SGM is honoured to be invited to become an affiliated organization to the scheme. A list of expert microbiologists willing to be consulted has been added to the SPSIS database.

If you are interested in becoming one of the advisers, contact Faye Jones (email pa@sgm.ac.uk) for details.

ABOVE:
Pilot whales swimming offshore in Tenerife.

BOTTOM RIGHT:
Goldfish ulcer disease caused by an atypical strain of *Aeromonas salmonicida*.

PHOTOS B. AUSTIN

Aquatic microbiology

Brian Austin

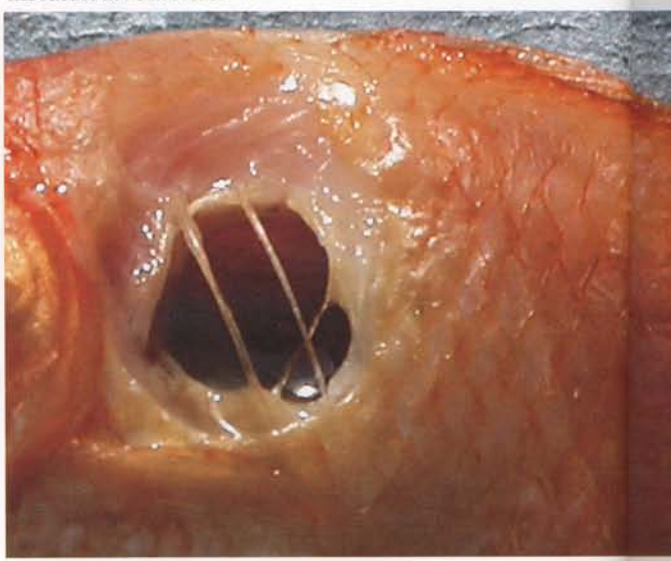
The UK, especially Scotland, has a long history of research and teaching/training in aquatic microbiology. For example Dr Jimmy Shewan, late of the Torry Research Station in Aberdeen, was a force behind the development of modern marine microbiology in the UK by emphasizing fish spoilage microbiology and what would now be described as an understanding of the biodiversity (= taxonomy) of bacteria in the sea. Jimmy was a noted teacher, and, among his other accomplishments, directed the postgraduate research activities of aspiring microbiologists, including John Liston, who subsequently departed our shores for the USA, and in turn trained Rita Colwell (the former Director of the National Science Foundation, USA). Rita has continued the trend by training many of the current generation of marine microbiologists worldwide.

Researchers have featured pollution microbiology and in particular the fate of pathogens in the aquatic environment, with the current debate centring on the state of these organisms, i.e. are they culturable or non-culturable/dormant/damaged/senescent? Interest in fish spoilage continues with the recent observation in Heriot-Watt University that changes in technique (use of different woods) can extend the life of smoked fish without impacting on flavour or texture, and reduce the survival of bacterial pathogens such as *Listeria monocytogenes*. Ironically, such woods contain compounds which are effective against multiple-antibiotic-resistant strains of human pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA).

On-going work on fish pathology has led to the recognition of new pathogens (e.g. *Pasteurella skyensis*) and developments in disease control strategies. Vaccines continue to be developed for an ever-increasing range of commercially important fish pathogens (e.g. for the control of ulcer disease in ornamental fish). Probiotics are offering potential to boost appetite, improve the overall health of animals and confer resistance against specific diseases, such as furunculosis which is caused by *Aeromonas salmonicida*. Yet unlike terrestrial agriculture, many probiotics considered for use in aquaculture are representatives of Gram-negative bacterial taxa. As a curious twist, there is evidence that some are as effective dead as alive. This raises the question about whether such preparations should be regarded as probiotics or oral vaccines (they induce innate immunity).

For the future, marine biotechnology offers the potential for wealth creation by the development of new and exciting products. Already, marine bacteria – inevitably from groups not usually associated with antimicrobial activity – have been found to produce novel pharmaceuticals, including anti-infectives [with activity against MRSA and vancomycin-resistant enterococci (VRE)], antiviral agents and antitumour compounds. Surfactants have been commercialized, of which one example is Emulsan (used to clean oil tankers), which is produced by a Gram-negative marine organism thought to be an *Acinetobacter*. This product has the added benefit of allowing the recovery of heavy metals, such as uranium from wastes. Consideration has been given to the use of bacteria to degrade the hydrocarbons in crude oil spills, although it seems unrealistic to expect any culture to make much headway against some of the more dramatic and extensive oil slicks which have occurred recently around the world's coastline.

The developments are certainly exciting – what will the future have in store?



Hot off the Press

Science writer Meriel Jones takes a look at some papers in current issues of the Society's journals which highlight new and exciting developments in microbiological research.

ABOVE RIGHT:
UV photography of *Agrobacterium*-infiltrated leaves of *Nicotiana benthamiana*. From left to right: non-infiltrated wild-type (control), and GFP expression constructs co-infiltrated with an empty binary vector, the influenza virus NS1 gene construct and an NS1rb mutant, respectively.
COURTESY M. PRINS, WAGENINGEN UNIVERSITY, THE NETHERLANDS

Silent defence

Over the last decade, RNA silencing has changed from a mysterious and obscure phenomenon to part of mainstream biology. It is a natural feature of virus resistance in plants and insects and also occurs in fungi and nematodes. It works through triggering the rapid degradation of specific messenger RNAs and hence preventing proteins being produced from particular genes. The presence of double-stranded RNA initiates the process, and such RNA molecules are a characteristic feature of many plant viruses, but few normal cell activities. This fact has been exploited by molecular biologists to develop methods for silencing any gene through creating ways of producing suitable complementary RNA within the cell.

While many researchers are investigating the details of gene silencing, two research groups have been asking a fundamental question about the process: does it occur in mammals? Gene silencing works in mammalian cells when researchers provide suitable RNA, so the cells must have all the molecular machinery. Double-stranded RNA has a major role in inducing the protective protein interferon in response to viral infections in mammalian cells, but there is no evidence that silencing of viral genes is a second defence mechanism. Many viruses contain proteins that are important in virulence, but the exact mechanism is frequently unknown. Now, reports from research groups in Spain and the Netherlands published in *Journal of General Virology* provide persuasive evidence that RNA silencing is also an antiviral defence response in mammals.

Their experiments rely on a well-established assay using the bacterium *Agrobacterium tumefaciens* and plants. The bacterium has been engineered to contain the gene for green fluorescent protein (GFP), designed to produce transient high levels of messenger RNA once the bacteria enter the leaf tissue. This should normally trigger the gene silencing response so that production of GFP dies away over a few days. If for any reason gene silencing does not occur, production of the green fluorescence should be sustained for weeks. Viruses have devised mechanisms to counteract many aspects of their host's antiviral defences, and some plant- and insect-pathogenic viruses have proteins that interfere with RNA silencing. There have been suggestions that mammalian viruses must be able to suppress gene silencing, but until recently no-one had produced experimental evidence for this.

Both research groups have investigated the multifunctional NS1 protein of the human influenza virus. It is important in virulence and is already known to have roles in ensuring preferential production of viral proteins by infected mammalian cells, interference with normal mammalian messenger RNA and preventing one of the interferon-mediated antiviral defences. It is a good candidate for suppressing gene silencing because it binds to double-stranded RNA *in vitro*. Researchers at the Centro Nacional de Biotecnología in Madrid led by Juan Antonio García added bacteria that contained the gene for NS1 to the assay system, and prolonged fluorescence showed that NS1 had rapidly suppressed any gene silencing within the leaf. As well as preventing this local silencing, the influenza virus protein also partly switched off the systemic silencing system that provides virus protection for the whole plant. When the researchers tested the effects of this silencing on a real viral infection of tobacco plants, the consequences could be lethal. In one series of tests, the control plants had a very mild infection while ones where NS1 had suppressed gene silencing were killed in 9 days.

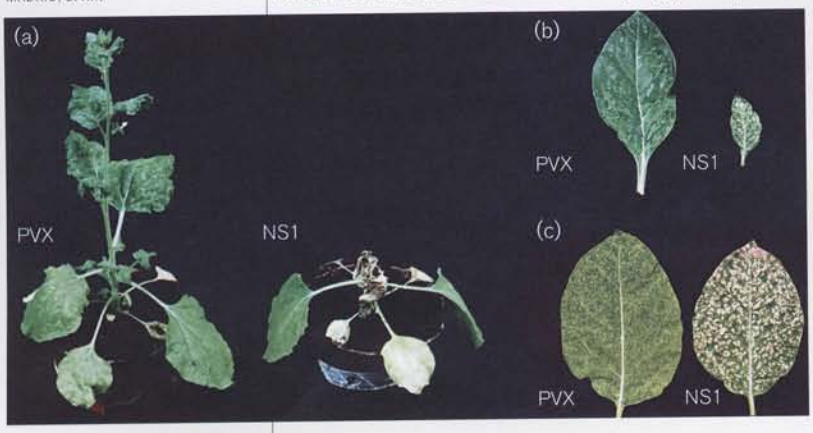
The mechanism of gene silencing requires the production of characteristic short pieces of RNA called small interfering RNAs (siRNAs). Researchers at Wageningen University in the Netherlands, in collaboration with the Viruvation company, wondered whether NS1 suppresses silencing by binding to siRNAs and hiding them from the gene silencing system. Their tests showed that NS1 could bind to synthetic siRNAs and natural ones extracted from plants very efficiently, and by testing mutant forms of NS1 they pinned down the region of the protein that did this job.

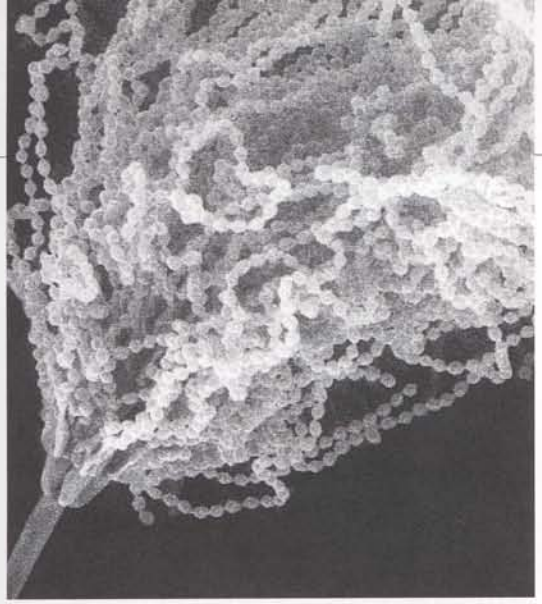
The idea that gene silencing is an important defence against virus infection in mammals as well as plants is therefore becoming more convincing. The final evidence will come from experiments in mammalian systems, and researchers are now designing the methods to do this. If it really does occur, this would provide a new approach to designing treatments for viral diseases.

Bucher, E., Hemmes, H., de Haan, P., Goldbach, R. & Prins, M. (2004). The influenza A virus NS1 protein binds small interfering RNAs and suppresses RNA silencing in plants. *J Gen Virol* **85**, 983–991.

Delgadillo, M. O., Sáenz, P., Salvador, B., García, J. A. & Simón-Mateo, C. (2004). Human influenza virus NS1 protein enhances viral pathogenicity and acts as an RNA silencing suppressor in plants. *J Gen Virol* **85**, 993–999.

BELOW:
Phenotypic effects after 20 days associated with the expression of NS1 protein from PVX vector in (a) *Nicotiana benthamiana*, (b) *Nicotiana clevelandii* and (c) *Nicotiana tabacum*. Plants were agroinfiltrated with PVX vector containing no insert (PVX) or containing the NS1 gene (NS1). Tissues inoculated with PVX-NS1 show severe necrosis.
COURTESY J. A. GARCÍA, CSIC, MADRID, SPAIN





New antibiotics from the rain forest

Antibiotics are one of the big successes of the 20th century. They provide treatment for infections that would otherwise be fatal. The first antibiotic came from a fungus, but nearly 75 % of the world's current antibiotics are from one group of bacteria, the streptomycetes. In addition to treating bacterial infections, compounds isolated from streptomycetes are now used in treatments for cancer and conditions such as high blood pressure.

Most of the streptomycetes that produce useful compounds come from soil, but researchers working with Gary Strobel at Montana State University in the USA have turned to a different source of biodiversity, namely the rain forests of the Amazon, in a search for new compounds with new biological activity. Instead of soil, they have looked for microbes that live inside plants without causing any negative effects, known collectively as endophytes. Scientists suspect that most plants contain bacterial or fungal endophytes but little is known about them.

Strobel and his co-workers isolated a streptomycete from a *Monstera* vine in the Lake Sandoval area of the Bahuaja Sonene Park Nacional in the upper Amazon region of Peru. Their key interest was whether it produced compounds with biological activity, so they grew the bacteria in the laboratory and concentrated the waste growth medium. They used high-resolution chromatography to separate the compounds in the mixture, and checked each one for activity. The initial tests investigated whether the compounds could inhibit the growth of a range of organisms. One compound, although it did not inhibit the growth of bacteria, was as effective as the best antimalarial drug against *Plasmodium falciparum*, the causal agent of malaria. It also inhibited the fungus *Pythium ultimum*, an important pathogen of plants. Importantly, it was relatively non-toxic to human cells.

The researchers obviously wanted to know what this compound was and used a series of physical chemical methods to identify it. The single chromatographic peak turned out to contain several very similar compounds. All were made from the three amino acids methionine, tyrosine and leucine, along with a fatty acid and two other components that were probably also amino acids. This small peptide is unlike any that are already known, so the researchers have discovered a new type of bioactive compound that may one day lead to new treatments against a range of human or plant pathogens.

Ezra, D., Castillo, U. F., Strobel, G. A., Hess, W. M., Porter, H., Jensen, J. B., Condron, M. A. M., Teplow, D. B., Sears, J., Maranta, M., Hunter, M., Weber, B. & Yaver, D. (2004). Coronamycins, peptide antibiotics produced by a verticillate *Streptomyces* sp. (MSU-2110) endophytic on *Monstera* sp. *Microbiology* 150, 785–793.

A 'harmless' killer

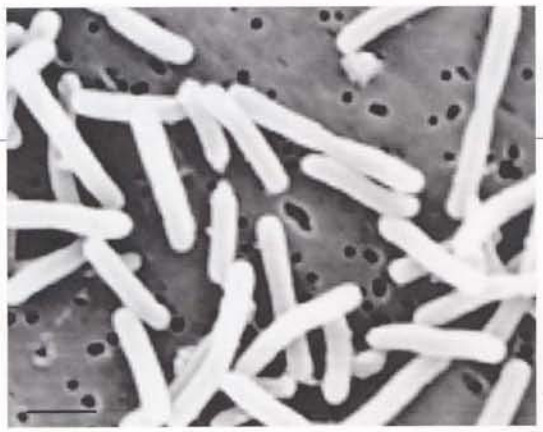
Species of *Lactobacillus* live in many habitats, including the gastrointestinal tract. Their presence has beneficial effects such as protection against pathogens and stimulation of the immune system. Indeed, lactobacilli are used in making several fermented foods, including yoghurt and sauerkraut. The genus is not considered pathogenic and clinical reports of lactobacilli in infections are generally attributed to contamination. Patients with infections that are genuinely caused by lactobacilli are usually suffering from illnesses that require immunosupressive therapy or antibiotic treatment that could have caused atypical behaviour in the bacteria.

However, researchers in Portugal have reported a serious *Lactobacillus* infection in a 53-year-old patient with a history of rheumatic fever, but no problems with his immune system. His diet included several yoghurts every day, and 3 months after having a tooth extracted he was suffering from a fever with muscle and joint pains. He was admitted to hospital, and treated with antibiotics for the bacterial infection that was detected in his blood and bone marrow. The fever continued, and a heart murmur caused the physicians to change the antibiotic regimen and make further tests. They became convinced that the man had bacteria growing on a heart valve, and as his condition deteriorated, they decided to replace the valve. Finally, 8 months after surgery, the patient was fully recovered.

One of the problems was the difficulty in identifying the infection. Only one type of bacterium was isolated from all the clinical samples, including the heart valve. Although its antibiotic sensitivity could be measured, and used to guide treatment, it could not be identified properly with conventional clinical laboratory tests. In the end, researchers isolated DNA from the bacterium and used the sequence of the 16S rDNA to confirm its identity as *L. casei*, a species usually considered completely non-pathogenic. This example of serious illness caused by an unusual organism indicates how clinicians need to be alert for risks associated with specific individual clinical histories.

Zé-Zé, L., Tenreiro, R., Duarte, A., Salgado, M. J., Melo-Cristino, J., Lito, L., Carmo, M. M., Felisberto, S. & Carmo, G. (2004). Case study of aortic endocarditis caused by *Lactobacillus casei*. *J Med Microbiol* 53, 451–453.

TOP LEFT:
Sporophore of *Streptomyces* sp. MSU-2110. This verticillated micro-organism is endophytic on *Monstera* sp., a vine that inhabits the rainforest of the upper Amazon region of Peru. The organism produces coronamycin, which has bioactivity against the malarial parasite as well as a number of plant-pathogenic fungi. The photograph was taken with the aid of an environmental scanning electron microscope and shows the spore masses attached to the verticels.
COURTESY W. M. HESS, BRIGHAM YOUNG UNIVERSITY, AND G. STROBEL, MONTANA STATE UNIVERSITY, USA



An end to red tides?

Red tides are natural events in warm, usually polluted, coastal waters. The population of unicellular algae in the seawater increases so much that the water turns bright red because of the number of cells. The red colour is due to photosynthetic pigments in the algae. The problem is that many of the algae secrete toxins into the seawater that are harmless to shellfish, but can poison fish and humans. There is therefore considerable interest in ways to prevent these algal blooms. Some bacteria can kill algae and might be developed into a control method.

Researchers from Korea led by Sang-Jin Kim at the Korean Ocean Research and Development Institute isolated a new species of bacterium from the surface water of Masan Bay in Korea during a red tide. It could kill and lyse several species of marine microalgae, and the researchers have now discovered that it belongs to a completely new genus of bacteria and have named it *Kordia algicida* after the Institute and its algal killing ability.

To determine whether it was indeed a new species, the researchers extracted DNA from the bacterium and obtained the sequence of its 16S rDNA. This region has been sequenced from thousands of bacterial species, but none was very similar to this bacterium. The most closely related species were in the family *Flavobacteriaceae* so it had to be the first representative of a new genus. When the researchers tested the growth requirements and physiology of the bacterium, these were also distinctly different from its neighbours within the *Flavobacteriaceae*. Whether *K. algicida* will be useful for controlling red tides will only be known after further investigation.

Sohn, J. H., Lee, J.-H., Yi, H., Chun, J., Bae, K. S., Ahn, T.-Y. & Kim, S.-J. (2004). *Kordia algicida* gen. nov., sp. nov., an algicidal bacterium isolated from red tide. *Int J Syst Evol Microbiol* 54, 677–682.

ABOVE:
Scanning electron micrograph of *Kordia algicida* strain OT-1[T]. Bar, 1 µm.
COURTESY SANG-JIN KIM, KOREA OCEAN RESEARCH AND DEVELOPMENT INSTITUTE, ANSAN, KOREA

Microbiology 150

To celebrate the 150th volume of *JGM/Microbiology*, a reunion of Editors-in-Chief was held at the Society Dinner in Bath. Pauline Meadow (1981–1985), Derek Smith (1985–1990), John Freer (1990–1995), Jon Saunders (1995–2000) and Chris Thomas (2000–) were joined by Hilary Watson (Bower) (Editorial Secretary 1975–1982) and Chris Sinclair (Editorial Secretary/Managing Editor 1982–) for an evening of editorial reminiscences. Unfortunately their predecessors John Postgate, Stuart Glover and Eddie Dawes were unable to attend.

In case you were wondering – no, the journal is not 150 years old! It was founded in 1947 but had more than one volume per year from 1952 to 1981.

From left to right: (*standing*) Pauline Meadow, Derek Smith, John Freer, Jon Saunders, Chris Thomas, (*sitting*) Hilary Watson (Bower), Chris Sinclair. (PHOTO IAN ATHERTON, SGM)

Antibiotic resistance and bile

Bacteria belonging to the genus *Salmonella* cause diseases like food poisoning and typhoid fever. They infect the digestive tract, including the small intestine and gallbladder, which contain bile and bile salts. These are detergents, derived from cholesterol, which the body secretes to aid digestion of fats. Concentrations regularly reach up to 2 % in the intestine and 8 % in the gall bladder. All detergents are antimicrobial compounds and bile is particularly potent. One reason why people who are malnourished are more susceptible to intestinal infections is that they lack bile. Bacteria that live in this environment must be able to survive bile's toxic properties, and microbiologists have used bile resistance as one way to selectively isolate this type of bacterium. *Salmonella typhimurium* can grow on media that contain up to 60 % bile, substantially higher than would ever be encountered naturally.

Researchers have been discovering that bacteria exploit bile as a signal that they are in a particular region of the digestive tract. As a consequence, bacterial cells switch on a number of characteristics that make them better able to survive in this environment. The full number is unknown, but includes better adhesion and invasion of the intestinal cells and increased resistance to antibiotics, as well as a pump to expel bile from the bacterial cell. Recent work, led by John S. Gunn at Ohio State University, as well as researchers at the University of Texas and Stanford University, has added to information about the detection of bile by *S. typhimurium*. The researchers used DNA microarrays to compare the activity of all the genes in this species in the presence and absence of bile. Three genes, *marR*, *marA* and *marB*, stood out as among the most affected, and suggested a way to link antibiotic resistance to the presence of bile.

The *marR*, *marA* and *marB* genes are found next to each other on the *S. typhimurium* chromosome. They were known to be involved in resistance to a number of antibiotics, such as chloramphenicol and tetracycline. *marR* encodes a protein, MarR, which stops production of the MarA and MarB proteins. The researchers discovered that one specific bile salt, deoxycholate, could bind to the MarR protein and prevent its interference with MarA and MarB production. However, the effect of these genes on bile and antibiotic resistance turned out to be more complicated than expected.

MarA is known to affect the activity of further genes, while the role of MarB is unknown. Although one of the antibiotic expulsion systems that MarA is thought to control (AcrAB) is essential for resistance to bile, it is not switched on by MarA. When the researchers deleted *marR* and *marA* from a strain of *S. typhimurium*, the bacteria survived a lethal concentration of bile equally well and were almost as resistant to the chloramphenicol. Other systems that can control AcrAB turned out to be unaffected by bile. The genes regulated by MarA remain unknown, but are likely to play a role in survival of *S. typhimurium* during infection. In addition, there must be systems in *S. typhimurium* to switch on the AcrAB efflux system in the presence of bile that remain to be discovered.

Prouty, A. M., Brodsky, I. E., Falkow, S. & Gunn, J. S. (2004). Bile-salt-mediated induction of antimicrobial and bile resistance in *Salmonella typhimurium*. *Microbiology* 150, 775–783.

Another step towards a cervical cancer vaccine

Epidemiological studies have shown that human papillomavirus type 16 (HPV-16) is the main cause of cervical cancer. This cancer kills around 400,000 women in the world every year and it might be possible to prevent or treat infections with a vaccine. A recent trial of a vaccine designed against the surface of the virus showed a significant reduction in both viral infection and cancer. Researchers in France and Mexico have been collaborating to design a vaccine against a protein produced during infection with HPV-16 because this could lead to an effective therapy for women who are already infected.

The researchers chose the viral protein E7 because it is essential in the process that transforms normal human cells into cancerous ones, and assessed the immune response of mice to several systems for delivering it. All were based around using a living bacterium, *Lactococcus lactis*, which is generally considered harmless, and is used in the food industry. It survives transiently in the human gut and could be a low-cost method of administering the vaccine using a mucosal route. The researchers designed strains of *L. lactis* to produce the viral E7 protein at different levels and locations within the bacterial cell to see how the immune response was affected. A drop of bacterial culture was placed in the nose of each mouse at fortnightly intervals for a month, and then the researchers measured the immune response in the animals. Production of E7 was triggered with a chemical immediately before the inoculation because the first experiments showed that this led to a higher immune response.

The mice that had been immunized with bacteria that synthesized E7 attached to the bacterial cell wall, rather than secreting it or retaining it within the cell, showed the greatest immune response. These bacteria synthesized the most E7, as well as possibly making it most accessible to the immune system. Although these experiments are a long way from a vaccine for humans, they are one step towards development of a safe and effective treatment.

Bermúdez-Humarán, L. G., Cortes-Perez, N. G., Le Loir, Y., Alcocer-González, J. M., Tamez-Guerra, R. S., Montes de Oca-Luna, R. & Langella, P. (2004). An inducible surface presentation system improves cellular immunity against human papillomavirus type 16 E7 antigen in mice after nasal administration with recombinant lactococci. *J Med Microbiol* **53**, 427–433.

A novel species of *Mycobacterium* involved in non-tuberculous lung disease

Mycobacterium tuberculosis causes tuberculosis, most frequently in the lungs. There are several related species that can also cause disease, and detection and identification is crucial to providing appropriate treatment. Organisms of the *Mycobacterium avium* complex (MAC) are the non-tuberculous mycobacteria species most often isolated in clinical laboratories. Although most of these species are not considered pathogenic, they can cause chronic lung disease in older individuals as well as disseminated disease in immunocompromised patients. Now that a commercial nucleic acid probe identification kit is available, easy, accurate and rapid identification of MAC species is possible, in contrast to previous biochemical tests.

Researchers at the National Reference Centre for Mycobacteriology in Manitoba have collaborated with colleagues across Canada to review information on atypical MAC strains and in the process have singled out a new, pathogenic species. This work was prompted by the case of a 72-year-old woman who had suffered from recurring chest infections for 52 years. After she ended up in hospital with pneumonia in 1990, a series of investigations was carried out, including computed tomography scans and repeated attempts to obtain a causal organism from her sputum. Recurring bouts of illness, difficulties with her lungs, and surgery continued throughout the decade. At one point, a mycobacterium, *M. gordonae* was identified in her sputum samples. This is a frequent member of the microbial flora that lives on the human body, so was not considered to be relevant to the woman's illness. Finally, in August 2000 she became very seriously ill and MAC bacteria were finally identified in her lungs using the nucleic acid probe method. She was treated with appropriate antibiotics, and her condition rapidly improved.

One of these MAC strains was investigated at the National Reference Centre for Mycobacteriology, looking both at its DNA sequence and physiological properties. The strains grew at between 25 and 37 °C, but were unable to grow above 42 °C. Although the bacterial colonies were initially transparent, they developed a bright yellow colour after the first two weeks, a property termed scotochromogenicity. Testing for antibiotic sensitivity indicated that although the strain was resistant to isoniazid, it was sensitive to many others, including rifampicin, streptomycin and linezolid.

The DNA sequence, although close to that of *M. interjectum*, differed from other mycobacterial species. A strain isolated from the woman in 1999 as *M. gordonae* had the same sequence, indicating that she had had a prolonged infection with the organism. This showed how the results of biochemical testing had been misleading. It turned out that more than a dozen strains examined at the Laboratoire de Santé Publique du Québec had the same physiological and DNA features.

The consistent characteristics of this group of 16 isolates, and their obvious association with disease, have led the researchers to propose naming them as a new species, *M. saskatchewanense*, to draw attention to its possible presence in unusual lung infections.

Turenne, C. Y., Thibert, L., Williams, K., Burdz, T. V., Cook, V. J., Wolfe, J. N., Cockcroft, D. W. & Kabani, A. (2004). *Mycobacterium saskatchewanense* sp. nov., a novel slowly growing scotochromogenic species from human clinical isolates related to *Mycobacterium interjectum* and Accuprobe-positive for *Mycobacterium avium* complex. *Int J Syst Evol Microbiol* **54**, 659–667.

SGM Symposium Volume 63 review

Microbe–Vector Interactions in Vector-borne Diseases

SGM Symposium Vol. 63

Edited by S.H. Gillespie, G.L. Smith & A. Osbourn

Published by Cambridge University Press (2004)

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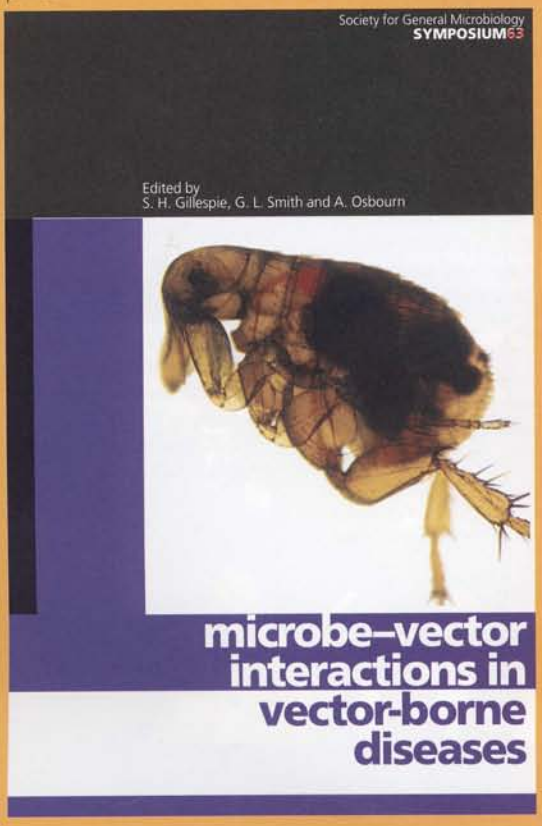
Members: £30.00/US$50.00

pp. 383. ISBN: 0-521-84312-X

Symposia proceedings usually have both strengths and weaknesses as demonstrated by this particular volume. Strengths include up-to-date comprehensive reviews by individuals selected for their expertise, offset by patchy coverage of the entire subject matter. The latter is to be expected since scientific symposia are often constructed around themes and availability of speakers, but it is nevertheless frustrating when the title suggests the expectation of a comprehensive overview.

The opening chapter provided a succinct introduction to vector-borne diseases of man, from viruses, bacteria, rickettsiae, protozoa and nematodes, including a useful summary of burden of disease estimates, leading the reader to expect a systematic approach to the subject. Instead what follows is a pot-pourri of chapters picking out areas of work that illuminate the field, but not always progressing logically. There is a strong overall bias towards discussion of viral vector-borne diseases with odd chapters on *Borrelia*, *Yersinia* and *Anaplasma phagocytophilum*, reminding us of the importance of bacterial vector-borne disease, but not really covering it to the same depth. The single chapter dealing with nematode transmission of plant viruses sat rather uncomfortably in this volume which is aimed more at the human pathogen field, but it is nevertheless a sentinel indicator of plant vector-borne disease.

An order form for Symposium Vol. 63 (and earlier volumes in the series) appears on p. 109.



I found the chapter on tick-borne disease systems which followed the introduction particularly fascinating for the way that it brought together observational studies in biology/ecology with molecular epidemiology of tick-borne viruses to construct a geographical rationale for the diversity of tick-borne disease. It was disappointing not to find an equally lucid chapter on the diversity of mosquito-borne viral diseases, but perhaps all that this signifies is that the fusion of different scientific disciplines hasn't happened yet in this area. The sections on vector competence and immunity were comprehensive and the chapter on RNA-based immunity in insects enhanced the topicality of the reviews. These were complemented by chapters exploring environment influences on arboviruses and their vectors and how mosquitoes can exist with viruses, which together provided a useful summary of diverse areas of work.

Intervention strategies to interrupt human vector-borne disease are touched upon in the chapter on vaccines targeting vectors. There is also much exciting work on manipulation of vectors, including the generation of transgenic malaria using mobile genetic elements to target mosquito tissue-specific gene expression and interrupt malaria replication. However, there are many different genetic approaches, such as modification of symbiotic bacteria which act to clear parasitaemia of reduviid bugs carrying Chagas' disease, and similar approaches for tsetse flies and trypanosomiasis, which are not mentioned at all and would perhaps have been appropriate for this volume. Discussions of the fitness of genetically modified mosquitoes are interesting but limited and understanding the contribution of single gene mutation to complex organism fitness gain and the ecology of mosquito/vector species will be an important up-coming area of study. The debate on introducing genetically modified insects as a means of combating human disease is likely to stir a cauldron of views on genetic manipulation of the environment and more insights into this from the experts writing in this volume would have been pleasing.

Notwithstanding the critical remarks about patchy subject coverage, the book has a place in any laboratory studying microbe–vector interactions and will doubtless be valuable to undergraduates and postgraduates alike, as well as experienced workers and teachers. It falls short of being a comprehensive up-to-date reference text, but the price ensures that it should be easily accessible to many organizations and individuals.

As usual with SGM symposia volumes, the production quality is good and the illustrations are clear. The overall layout of the book could benefit from better organization to make the flow of chapters more coherent, but if this book is used as something to dip into and out of, this feature becomes less of an irritant, and the book is warmly welcomed as an addition to the bookshelf.

■ ***Maria Zambon, Health Protection Agency***

Obituary

Fred Brown

31 January 1925–20 February 2004

ABOVE:
Fred Brown, 1925–2004.
COURTESY ROGER BROWN

Members of the Society will be saddened to learn of the death of Fred Brown, FRS OBE, at the age of 79 on 20 February, 2004. With his passing we lose another of the 'old school' of virologists who have had a major impact on their chosen discipline over the past half century. Fred had a long and influential relationship with the SGM and was elected as an honorary member in 1991. He was Editor-in-Chief of the *Journal of General Virology* from 1975 to 1980 and was its most prolific single contributor.

Fred hailed from Burnley and was a Lancastrian through and through. After a brilliant career at Burnley Grammar School, of which he was school, cricket and football captain, he studied chemistry at the University of Manchester. Having obtained a first class degree he went on to study carbohydrate chemistry for his doctoral degree. After working for short spells at the Bristol University's Fruit and Vegetable Preservation Station, the Hannah Dairy Research Institute and the Christie Hospital, Fred joined the Foot-and-Mouth Disease Institute (as it was then) at Pirbright in 1955, where he launched a career in virology that spanned almost 50 years. There he established a molecular virology laboratory that rivalled the best in the world for FMDV research. His vision and energy inspired both the permanent staff at the Institute and a long list of national and international visitors. He left the Institute to join Wellcome Biotech as head of virology in 1983. He retired from Wellcome in 1990 and moved to the USA to continue working on FMDV at the USDA laboratory at Plum Island. He moved back to the UK just 5 weeks before his death.

Fred's training as a chemist left him with a passionate desire to understand the molecular details of the structure and function of viruses. When he entered the field of FMDV little was known about the fine detail of structure and composition of the virus. During his long career he saw this change dramatically, in a large part due to his own efforts, from one in which the number of proteins in the virus particle was unknown to the current situation in which the disposition of (nearly) all of the atoms in the virion is known, as is the precise nucleotide sequence of the genomic RNA of many serotypes and strains. Just a few of the many steps along this path to knowledge in which Fred was directly involved include: demonstration of the infectivity of the viral RNA, unravelling the antigenic structure of the virus, determining nucleotide sequences of the viral RNA and the crystal structure of the virus particle. Although we have come a long way, Fred would be the first to admit that we still have a long way to go and he was still involved in FMDV research until a few weeks before his death. Fred is best remembered for his Olympian status in the FMDV world, but he also had broader virological interests. For example, he was particularly supportive of the International Committee for the Taxonomy of Viruses which he served from 1968 until 1987, being President from 1981 to 1987.

Although devoted to fundamental research, Fred was always keen on maximizing the practical application of his findings. For example, he pioneered the development of alternatives to formaldehyde as the inactivating agent for FMD vaccines, so providing the means to eliminate the risk posed by residual live virus. Much later he demonstrated through molecular 'detective' work that an outbreak in northern France in 1981 was, in fact, due to improperly inactivated vaccine. He studied viruses such as VSV, VEV and SVDV that could be clinically confused with FMD in part to improve differential diagnosis. He was always interested in vaccine development and became deeply involved in attempts to revolutionize vaccine production using synthetic peptides.

Fred was always a man of strong views and convictions (a typical northerner) which were usually bluntly expressed. These characteristics made him a valued committee member and he was asked to serve on many, such as the Tyrrell committee on Bovine Spongiform Encephalopathy. He was elected as a Fellow of the Royal Society in 1981 and he was awarded the OBE in 1999 in recognition of his service to British science. Fred did not moderate his opinions during the catastrophic UK outbreak of FMD in 2001 and was a strong advocate of vaccination; it is probably lucky that he was awarded his 'gong' before that tragedy emerged.

Fred was always highly supportive of young scientists and there are many British (and other) virologists currently enjoying successful careers who can look back fondly on their memories of Fred's support and generosity in their formative years. He is survived by his wife, Audrey, who is well known to many in the SGM, and their two sons, Roger and Bill.

Farewell, Fred.

● *Dave Rowlands is Professor of Molecular Virology in the Division of Microbiology, School of Biochemistry and Molecular Biology in the Faculty of Biological Sciences, University of Leeds, Leeds LS2 9JT, UK.*
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email: d.j.rowlands@bmb.leeds.ac.uk

Reviews

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RNAi: A Guide to Gene Silencing

Edited by G.J. Hannon
Published by Cold Spring Harbor Laboratory Press (2003)
US$130.00, pp. 436
ISBN: 0-87969-641-9

This volume describes the recently discovered phenomenon of post-transcriptional gene suppression mediated by short double-stranded RNA molecules. The phenomenon is widely believed to have evolved as a mechanism of genome defence against parasitic sequences, such as those from transposons and viruses. Even though the emphasis of the book is on the molecular mechanisms, the book does describe the use of RNAi in functional genomics. Over the last couple of years there have been numerous reports in the literature of the use of RNAi to inhibit viral infection of mammalian cells either by targeting viral RNAs or cellular RNAs encoding viral receptors. Unfortunately, however, these are not mentioned in this volume. This book would be useful to all those interested in the mechanisms and applications of RNAi, students and experienced researcher alike. The price would, however, restrict its purchase to institutions.

■ ***Christopher Ring***
Glaxo SmithKline R&D, Stevenage

MRSA: Current Perspectives

Edited by Ad.C. Fluit & F.-J. Schmitz
Published by Caister Academic Press (2003)
US$180.00/£90.00, pp. 365
ISBN: 0-9542464-5-4

MRSA is probably the most widely recognized bacterium by the man in the street, so this monograph is likely to be of interest to many microbiologists. Because of recent advances, it concentrates on the genetic basis of antibiotic resistance and virulence in MRSA. As there are only short chapters on the control and treatment of MRSA infections, it is not a practical manual. The chapters dealing with the molecular evolution and mechanisms of methicillin resistance in *Staphylococcus aureus* are both comprehensive and clearly written and would be ideal for the interested undergraduate/graduate student or lecturer wishing to update themselves. There are several good smaller specialist chapters, on VISA and molecular typing, and another on small colony variants which does not seem to sit well with the rest of the book. My other criticism is that the Editors have allowed substantial overlap in the description of the genetics of methicillin resistance in chapters 3, 6 and 7. Overall, this is both a timely and comprehensive monograph bringing together important information which can be read and understood at a basic or advanced level.

■ ***Peter Hawkey***
HPA, West Midlands Public Health Laboratory, Birmingham

Human Immunodeficiency Virus – Human Virus Guides 2

Edited by D.D. Richman
Published by International Medical Press (2003)
US$85.00/£49.99, pp. 344
ISBN: 1-901769-09-7

This is a well laid out book, the text is complemented by background 'boxes' that explain underpinning techniques and concepts. The book is lavishly illustrated – the clear, detailed graphics make it both visually attractive and easy to read. Although all bases are covered – from molecular biology to social and ethical issues – the emphasis is on the clinical aspects. The sections on molecular and cellular biology, although generally accurate and up-to-date, lack depth. I believe therefore that it will be of most use to medical students and clinicians, and is unlikely to find its way into the reading list of basic science students. However, there is something for everyone here; anyone new to the HIV field and wishing to find out the latest information would find it a useful first point of call. For this reason it would make a useful addition to institutional libraries, particularly those in medical schools.

■ ***Mark Harris***
University of Leeds

Publisher's website addresses

Academic Press	www.academicpress.com
American Society for Microbiology	www.asmpress.org
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World Scientific Publishing	www.wspc.com.sg

The Microbial Models of Molecular Biology: From Genes to Genomes

By R.H. Davis
Published by Oxford University Press (2003)
£30.00, pp. 337
ISBN: 0-19-515436-3

Rowland Davis is a fungal geneticist who reminds us that microbial genetics started with *Neurospora*, not *E. coli*. In his account of its history, model organisms experience the rigours of Darwinian selection: '*The days of fungi as universal model organisms darkened as E. coli and bacteriophages emerged into the light*. Especially telling is the rise of yeast genetics, after the early maverick influence of Carl Lindegren, shaking off its past around 1970 and becoming a 'supermodel', one of only two according to Davis's definition, the second being *E. coli*. Other bacteria barely appear after 1970, so we read nothing about the genetic dissection of pathogenesis, symbiosis, antibiotic production or any of the other wonders of the second kingdom of life. The book, though, is finely researched; it should be in any library, reflecting varying views on the phenomenal rise of genetics in the second half of the 20th century.

■ ***David Hopwood***
John Innes Centre, Norwich

Antigenic Variation

Edited by A. Craig & A. Scherf
Published by Academic Press (2003)
£69.95, pp. 464
ISBN: 0-12-194851-X

This book examines how microbes vary the epitopes on their surfaces to avoid the host's immune response. It provides an excellent review, drawing from examples as diverse as HIV, *Haemophilus influenzae* and *Giardia lambia*.

I particularly liked the way the Editors did not restrict themselves to discussing mechanisms in just one group, such as bacteria, and I also appreciated the overview of mechanisms of antigenic variation, which I can see I will be referring to repeatedly as it draws together a broad range of publications in one straightforward chapter. I would recommend this text to anyone involved with vaccine and drug development, as well as those studying the host–microbe interaction: a useful addition to the bookshelf.

■ ***Petra Oyston***
Dstl, CBS Porton Down

Tuberculosis: The Microbe Host Interface

Edited by L.S. Schlesinger & L.E. DesJardin
Published by Horizon Scientific Press (2003)
US$180.00/£90.00, pp. 281
ISBN: 0-9545232-1-0

I loved this book; it provided exactly what I wanted. Over the last 10 years tuberculosis research has become fashionable again with a resulting exponential increase in the numbers of papers and new techniques. It is impossible to keep up. This book provided chapters that are relevant to the subject and contain a balance between literature review, technical description and interpretation of results. Individual chapters are well written and easy to read. The references are up-to-date, but more importantly, for a subject with more than 100 years of research behind it, seminal papers from the past are quoted rather than their conclusions referenced to review articles. In some instances this had the effect of emphasizing how flimsy the basis of some tuberculosis dogma is. My only substantive criticism was that the chapters sometimes lacked a clinical context, but now I am carping. This book is highly recommended to individuals who wish to update themselves on current methods and research in tuberculosis host–pathogen interactions.

■ ***Stephen H. Gillespie***
University College London

E. coli Plasmid Vectors: Methods and Applications. Methods in Molecular Biology, Vol. 235

Edited by N. Casali & A. Preston
Published by Humana Press (2003)
US$99.50, pp. 316
ISBN: 1-58829-151-0

This is a laboratory guide to the biology of plasmids and their role in genetic manipulation. There is good coverage of various types of vector and their manipulation and application in various situations, together with descriptions of various ancillary techniques for analysis of recombinants. The content is much more diverse and inclusive than the title might suggest, embracing for example sections on cloning in phage l vectors, site-directed mutagenesis and the purification of recombinant proteins. The volume contains very clear practical instructions and trouble-shooting guides that are both easy to follow and comprehensive. The background material is covered in sufficient detail to understand the theory behind the various protocols employed. There is a good selection of informative diagrams and quantitative information necessary to optimize methods. The book will be a very useful addition to laboratories investigating plasmids per se, and for those employing plasmids as vectors for gene cloning.

■ ***Jon Saunders***
University of Liverpool

Food Safety: Contaminants and Toxins

Edited by J.P.F. D'Mello
Published by CABI Publishing (2003)
£80.00/US$145.00, pp. 480
ISBN: 0-85199-607-8

This book aims to provide a global perspective on scientific documentation of recent advances, with guidance on future directions, in all matters relating to food safety. A substantial task! Three major sections cover biotoxins (plant, bacterial, shellfish, fungal), anthropogenic contaminants (pesticides, PCBs, dioxins, PAHs, heavy metals, nitro-compounds, veterinary products, adverse reaction to additives, contact migration of compounds) and case studies (prions, GM foods, radionuclides). The Editor concludes by pointing up continuing concerns. Overall the chapters are scientifically excellent, well poised for their target final year first degree student audience, although better indexing would further improve their usefulness. The book's aims have been achieved to a large extent, although one disappointment is that contributors are virtually exclusively from North America and Western Europe with just one from Japan which does lead to some bias in perspective. That said, it is strongly recommended as a well written, well priced library purchase.

■ ***Martin Collins***
The Queen's University of Belfast

Making Genes, Making Waves: A Social Activist in Science

By J. Beckwith
Published by Harvard University Press (2002)
£18.50, pp. 242
ISBN: 0-674-00928-2

Jon Beckwith's distinguished career as a bacterial geneticist, most of it at Harvard Medical School, spans four decades. Areas in which he has made notable contributions include the recognition of the promoter as separate from the operator and the former's involvement in catabolite repression, the development of gene fusion methodology, and the genetic analysis of secretion pathways. But, alongside his scientific activities, he has also been involved over those decades in many of the *causes célèbres* where science meets the social/political world. An early instance: the isolation by his group of purified *E. coli lacZ* DNA – accomplished without use of restriction endonucleases – remains a remarkable achievement, though quickly outstripped by technical advance, and led in 1970 to the ASM's Eli Lilly Award; in his prize speech, Beckwith announced that he would give the prize money to the Black Panthers (*Bact Rev* 34, 222). He has regularly protested against overly biological interpretations of human activity – the association of the XYY chromosomal make-up with predisposition to criminality, or the sociobiological interpretation of male aggression and the position of women in society – pointing to the results of putting eugenic theories into practice, not only in the Nazis' race theories, but also in the sterilization policies of many US states and European countries in the first half of the 20th century. Beckwith's style is sober and self-deprecating; he often admits earlier naïvety, and scrupulously examines his motives. By the end of the book, he has earned the reader's respect even if not always their agreement. If you're a young scientist troubled by aspects of the science/society thing and would like a role model, read this book to see how it's done.

■ ***Simon Baumberg***
University of Leeds

Natural Pathogens of Laboratory Animals: Their Effects on Research

By D. G. Baker
Published by American Society for Microbiology (2003)
US$119.95, pp. 397
ISBN: 1-55581-266-X

Research using laboratory animals is always potentially affected by the microbiological status of the animals themselves. This is true for many disciplines, but especially so when researching into infectious diseases. The mere presence of certain microbes in the experimental animals, without even causing overt disease, can be a disaster for measuring the outcomes of infection experiments and attendant immune responses. This book provides an excellent Introduction and first chapter concerning issues of husbandry and pathogen surveillance, and then ten more chapters, each in turn dealing with the pathogens of a different laboratory animal. The material is comprehensive and backed up by extensive lists of references. It is by no means a book to be read from cover to cover, but is an excellent reference source that should be part of the library of every laboratory animal facility and, dare I say it, every named vet and Home Office inspector.

■ ***Duncan Maskell***
University of Cambridge

New Aspects of CMV-Related Immunopathology, Monographs in Virology, Vol. 24

Edited by S. Prösch, J. Cinatl & M. Scholz
Published by Karger (2003)
Euro134.50/CHF188.00/US$163.50, pp. 260
ISBN: 3-8055-7618-8

This volume in the *Monographs in Virology* series is a compilation of 18 chapters on CMV biology arising from a meeting held in Berlin in 2002. The title of the book is somewhat misleading since half of the chapters deal with issues related to CMV pathogenesis and immunology, the other half address novel strategies in HCMV diagnosis and therapy. Not surprising for a book based on a meeting, the chapters are a mixture of style and content. Most fit the format of short reviews and highlight recent developments in CMV biology including CMV and atherosclerosis, evasion of the immune response, virus latency, role of tegument proteins, the latest on antivirals and approaches to studying CMI responses to CMV. All in all a volume providing something for everyone in this field and a useful reference source for those looking for updates on CMV.

■ ***Tony Nash***
University of Edinburgh

Ebola and Marburg Viruses: A View of Infection using Electron Microscopy

By E.I. Ryabchikova & B.B.S. Price
Published by Battelle Press (2004)
US$65.00, pp. 230
ISBN: 1-57477-131-0

This book describes a *tour de force* of investigating filovirus infections in tissue culture cells and *in vivo* using electron microscopy. Despite the use of a single technique, a comprehensive description of the effects of infection are given. The *in vivo* investigations consider both infected tissues and also secondary sites where the pathogenic effects of infection can be seen. The presentation is a compilation of a large number of experiments with the appropriate details included giving the feel of an extended research report. The description of the process of infection is supported by the inclusion of a large number of electron micrographs, though these cannot do justice to the volume of original data referred to. Inevitably, this book will appeal more to the specialist reader, despite the inclusion of an introductory chapter aimed at the non-specialist and attempting to explain virological terminology which seems a little misplaced in such a text.

■ ***Andrew Easton***
University of Warwick

When Food Kills: BSE, *E. coli* and Disaster Science

By T. Hugh Pennington
Published by Oxford University Press (2003)
£25.00, pp. 236
ISBN: 0-19-852517-6

This book is a fascinating read, packed with wry observations of human social behaviour, in potentially and actually disastrous circumstances arising from human weakness, particularly in regulatory authorities and inspectorates. Hugh Pennington is well qualified to comment on these failings, having chaired an Expert Group investigation into the 1996 outbreak of lethal *E. coli* O157 disease in Wishaw, Lanarkshire. The well-known food-related 'disasters', *E. coli* O157, BSE and foot-and-mouth disease, are just some of the scenarios considered (others include the Piper-Alpha oil rig, Aberfan and the airship R101), and the author dissects the common threads of human failure involved. This is not microbiology, but the social and political failings that contribute to such events are potential pitfalls for many in our discipline. The book is informative and thought-provoking and I recommend it highly for any who might be under the spotlight next time there is a microbiological disaster – which there will be!

■ ***Charles Penn***
University of Birmingham

Gene Delivery to Mammalian Cells. Vol. 1: Nonviral Gene Transfer Techniques. Vol. 2: Viral Gene Transfer Techniques. Methods In Molecular Biology, Vols 245 & 246

Edited by W.C. Heiser
Published by Humana Press (2003)
Vol. 1: US$99.50, pp. 320
ISBN: 1-58829-086-7
Vol. 2: US$125.00, pp. 584
ISBN: 1-58829-095-6

The ability to deliver foreign genes into mammalian cells has been hugely successful in allowing us to identify effects of the expression of new genetic information on cellular behaviour. Many effective experimental protocols have been developed for use on cells in culture. However, our ability to achieve gene delivery *in vivo* has lagged a long way behind, limiting the effectiveness of gene therapy as a way of treating disease. These two volumes cover a variety of viral and non-viral methods for the introduction of DNA into cells in culture and specific tissues *in vivo*. In a total of 59 chapters different authors provide a comprehensive survey of the protocols available. Those at the cutting edge of these technologies will already have their preferred methods, but the contents do provide insights into the choices available in this important area of biology and medicine.

■ ***Mike Clemens***
St George's Hospital Medical School, London

The Phylogenetic Handbook. A Practical Approach to DNA and Protein Phylogeny

Edited by M. Salemi & A.-M. Vandamme
Published by Cambridge University Press (2003)
£40.00/US$75.00, pp. 406
ISBN: 0-521-80390-X

This is a splendid book that does what it says on the cover and presents a practical approach to phylogeny with molecules. It is aimed at introducing the novice to the field, so is an excellent tutor for undergraduate or postgraduate study, or for anyone seeking to enter the field. There are many web addresses for downloads given in the text and there is always a danger that these will disappear during the useful life of the book, but most are well known, stable sites and readers should not have any difficulty building the test data sets or finding the latest version of the program under discussion. The text itself treads a well judged line between didactic instruction and exposing the reader to areas of uncertainty. As you will have deduced, having read this far, I was impressed and would recommend this book as a superb primer for the field.

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

How to Win the Nobel Prize: An Unexpected Life in Science

By J.M. Bishop
Published by Harvard University Press (2003)
£18.95, pp. 288
ISBN: 0-674-00880-4

Those who buy this book may be disappointed; those who perhaps would most enjoy it may not buy it. The title is misleading and evokes expectation of an account of Bishop's life and the work that culminated in his Nobel Prize. Not so. There is a brief resumé of Bishop's educational and scientific progress, interesting anecdotes surrounding the Prize itself, but very little about the actual work and the excitement surrounding the path of the award-winning science. There follow two splendid sections; an excellent historical perspective on the development of our understanding and control of microbe-borne diseases and a similar discourse on the nature and origins of cancer. I found these to be the gems within the book. They are written for and easily accessible to the non-scientist. Unfortunately the title gives no clue as to these treasures within.
The rest relates mainly to the politics of science. Drawing on the experiences of the author, the examples are exclusively American, giving a somewhat parochial impression to international readers. A mixture – but interesting.

■ ***John R. Arrand***
Institute for Cancer Studies, University of Birmingham

Dormancy and Low-Growth States in Microbial Disease. Advances in Molecular and Cellular Microbiology 3

Edited by A.R.M. Coates
Published by Cambridge University Press (2003)
£65.00/US$90.00, pp. 274
ISBN: 0-521-80940-1

Overall, this is an excellent addition to the literature in the area concerning *in vivo* growth in relation to microbial pathogenesis. The text provides a very comprehensive introduction to this subject, with the various chapters being extremely informative and well referenced. The majority of these chapters, covering topics such as environmental and host-associated stress, interbacterial signalling, biofilms and tuberculosis, are well written and easy to digest without sacrificing any depth. By necessity the Editor needed to select the chapter topics to maintain an overall theme. On first glance the final chapter on the resting states of seeds from higher plants might appear misplaced in a text primarily dealing with bacteria. However, in common with the short chapter covering yeast cell proliferation, this provides an interesting insight into the contrasting situation of dormancy in eukaryotic species. Certainly a worthwhile read for those looking to acquaint themselves with this field of research.

■ ***Andrew Lamb***
The Robert Gordon University, Aberdeen

Chromosomes: Organization and Function

By A.T. Sumner
Published by Blackwell Publishing (2003)
£29.50, pp. 287
ISBN: 0-632-05407-7

This admirable book exemplifies what can distil from depth of experience: in this case Sumner's years in what has now become the MRC Human Genetics Unit in Edinburgh. It balances molecular biology against what you can see; sequences, transcripts and proteins against staining and fluorescence imaging. The scope is appropriately wide: chromatin and chromosome structure, heterochromatin, sex chromosomes, imprinting, centromeres and chromosome segregation, telomeres, polytene chromosomes, and chromosomes in evolution and disease. The author asks straightforward questions – what is imprinting for and how do telomeres protect chromosome ends? – and provides the best answers available based on current knowledge, but is open about their frequent incompleteness. Molecular information is there when relevant to this goal, often related to microbial eukaryote examples, such as the detailed

section on centromeric DNA and proteins of *Saccharomyces cerevisiae*; but the reader will also learn a lot about how other systems – microbial, fungal, plant, animal – differ from the budding yeast paradigm. The strengths of this book are simplicity and directness, a consistently comparative approach, and a judicious summing up where no clear answer can yet be given (e.g. the role of imprinting; the relation between telomeres, ageing and cancer). The usual cliché that 'undergraduates would benefit from reading this book' is for once entirely justified – they might even be convinced that there are advantages in continuous text rather than bullet points. This is how science should be written; no-one teaching or thinking about genetics should be without access to it.

■ ***Simon Baumberg***
University of Leeds

Metabolic Engineering in the Post Genomic Era

Edited by B.N. Kholodenko & H.V. Westerhoff
Published by Horizon Bioscience (2004)
£90.00/US$180.00; pp. 456
ISBN: 0-9545232-2-9

The gene sequencing programmes have provided, in theory, all of the information necessary to create a complete *in silico* metabolic network capable of predictively modelling all cell functions. This has given a shot in the arm to the metabolic engineers who now have a much more comprehensive array of whole-cell models which can be used for developing their ideas. This book is an excellent collection of reviews by many of the key players. Even better might have been a textbook on the same subject with common structure and objectives throughout, but perhaps this is a tall order for such a rapidly-changing field.
Topics include: recent developments, proteomics, MRI tools, flux analysis, regulatory strength analysis, MetaCyc, expression modulation methods, a range of model-building techniques, and some predictions for future developments. However, the four examples of applications really demonstrate how metabolic engineering has blossomed in 21st century biology.

■ ***Mike Bushell***
University of Surrey

Biofilm Communities: Order from Chaos?

Edited by A. McBain, D. Allison, M. Brading, A. Rickard, J. Verran & J. Walker
Published by BioLine (2003)
Members (additional copy) £28.50 (UK only)/£30.00 (Europe)/£30.00 (ROW); Non-members £38.50 (UK only)/£40.00 (Europe)/£40.00 (ROW); pp. 429
ISBN: 0-9545756-0-1

This is the sixth in the series of volumes that have come out of the biennial meetings of the Biofilm Club held at Gregynog. As in previous volumes, members of the club offer papers which are then accepted, edited and organized within the meeting programme by the Editors. In this way an accurate snapshot is gained of who is doing what, and what is 'hot' at this stage of the subject's development. While the majority of presentations are from the UK, there are also a significant number from overseas.
The individual papers are of a uniformly high standard, and the publication as a whole has a very professional feel. Both applied aspects and fundamental studies of the nature of biofilms are included. In addition to technical papers dealing with methodology and with experimental studies of particular systems, there are also more reflective presentations focussing on concepts and models; altogether an eclectic mix.
The volume reflects well on the vigour of biofilm research, and on the prominent role played by many UK groups.

■ ***Allan Hamilton***
University of Aberdeen

Microbial Threats to Health: Emergence, Detection, and Response

By M.S. Smolinski, M.A. Hamburg & J. Lederberg
Published by The National Academies Press (2003)
£32.95, pp. 367
ISBN: 0-309-08864-X

As successor to the 1992 Institute of Medicine report *Emerging Infections: Microbial Threats to Health in the United States*, this book, not surprisingly, reads as a report with a strong American emphasis. The main body of text covers three key areas (emergence, detection and response to microbial threats) with a precise and thorough attention to detail. Though up to date with discussion on the ominous threat of the intentional use of microbes for harm, timing of publication has unfortunately not allowed discussion of the SARS outbreak. Frequent self-contained boxes of text offer interesting asides and provide a welcome break from the avalanche of information presented in the main text: did you know that hundreds of cases of coccidioidomycosis in California were linked to an earthquake? Though this publication is directed towards public health professionals, it will appeal to individuals with an interest in the wider challenges of infectious disease.

■ ***Sue Lang***
Glasgow Caledonian University

Infectious Diseases E-dition (Book/Website) Package, 2nd Edition

Edited by J. Cohen & W.G. Powderly
Published by Mosby/Elsevier (2003)
£283.00, pp. 2,700
ISBN: 0-323-02607-9

This book is monumental. Its two volumes, 247 chapters, 397 contributors and 2,487 pages weigh in at 4·4 kg. Even the index runs to 95 pages. So, what do you get for your money? Only the best and most comprehensive textbook of infectious diseases available in the UK today. The layout is clean, sharp and inviting. There is a liberal use of colour formatting for the different sections and the numerous (over 1,400) tables, illustrations, graphs and charts. The clinical pictures which include patients, X-rays, pathology specimens, etc., are frequent and instructive. The references, too many to count, are up-to-date and there is a generous number of relevant websites and other sources of electronic information. The amount of knowledge provided is overwhelming. After more than 20 years as a medical microbiologist I feel very ignorant. Can you name 54 complications of typhoid? Or 16 micro-organisms implicated in pneumonia or sepsis after near-drowning? Or how to properly follow up the traveller who has swum in Lake Malawi? Don't worry, this book has all the answers. *Infectious Diseases* was first published in 1999. This second edition contains a new chapter on bioterrorism and biodefense (*sic*) which includes disturbing pictures of a child developing smallpox. Emerging new syndromes such as West Nile fever are discussed for the first time. The book's illustrations are also provided on a free CD-ROM and there is access to an associated website. Every self-respecting medical microbiology library needs this book, having first made sure that its shelves are strong enough to carry it.

■ ***Paul Wright***
Conquest Hospital, St Leonard's-on-Sea

Vaccines, 4th Edition

Edited by S.A. Plotkin & W.A. Orenstein
Published by Saunders/Elsevier (2003)
£166.00, pp. 1,662
ISBN: 0-7216-96880

Having recovered from lifting this weighty (3·78 kg) tome, I found a wealth of information covering all aspects of vaccines. This included a discussion of general principles, manufacturing and validation schemes. In the current climate of emphasis on safety, the detailed consideration of technical issues will inform our understanding of the vaccines. Nor have authors neglected the history of vaccination. There is a timely inclusion of new vaccines, as they are introduced into clinical practice, e.g. Varicella, and details of current problems with established vaccines, e.g. Yellow Fever. Issues for particular staff and patient groups are addressed. The emphasis, not surprisingly in view of the contributors, is on US policy. I found it difficult to find a satisfactory coverage of MMR, of current UK interest (5 page references). Despite this, any serious departmental library will find this book an invaluable resource for senior scientists and clinicians.

■ ***Sheila M. Burns***
Specialist Virology Centre, Royal Infirmary of Edinburgh

Zoonoses: Infectious Diseases Transmissible from Animals to Humans, Third Edition

By H. Krauss, A. Weber, M. Appel, B. Enders, H.D. Isenberg, H.G. Schiefer, W. Slenczka, A. von Graevenitz & H. Zahner
Published by American Society for Microbiology (2003)
US$79.95, pp. 474
ISBN: 1-55581-236-8

This book provides a broad and concise, but limited, overview of zoonoses. The authors have included recent events such as the emergence of SARS, anthrax in bioterrorism and knowledge of the aetiology of prion diseases. Some zoonoses are covered more comprehensively than others and I was surprised that zoonotic clostridial infections were only briefly mentioned in an appendix. The book will interest public health practitioners, although some recent veterinary public health measures applied to control food-borne pathogens such as *Salmonella* and *Campylobacter* could have been expanded upon. Despite these minor criticisms, the book will be a readable reference text with

appendices that I found useful for quick reference. The book is reasonably priced and a useful addition to the reference bookshelves of university teaching departments and other public health organizations who require quick, basic information on particular zoonoses.

■ ***Chris Thorns***
VLA Weybridge

Quinolone Antimicrobial Agents, 3rd Edition

Edited by D.C. Hooper & E. Rubinstein
Published by American Society for Microbiology (2003)
US$125.95, pp. 500
ISBN: 1-55581-231-7

This latest edition should not come as a disappointment to those of us well versed in the 1st and 2nd editions. The book is well written by a number of respected authors and it makes an interesting read for 'quinolonophiles' because of new chapters that reflect the advances in quinolone research over the last 10 years since the 2nd edition. In particular, recent topics such as Q-T interval elongation (or not) with quinolones, the paediatric use of quinolones and the use of fluoroquinolones in community-acquired pneumonia are now covered. The target readership would be those individuals whose research requires an in-depth encyclopedia of the quinolones. I would also recommend that graduate students studying antimicrobial chemotherapy persuade their departmental librarian to get a copy.

■ ***Ian Morrissey***
GR Micro Ltd, London

Clinical Mycology

Edited by W.E. Dismukes, P.G. Pappas & J.D. Sobel
Published by Oxford University Press (2003)
£95.00, pp. 519
ISBN: 0-19-514809-6

Clinical mycology is an area of rapid advances and changing perspectives and so it is encouraging to see this new comprehensive text covering this field. The Editors have assembled an impressive list of authors who cover the ground first in a series of articles about antifungal drugs, then sections based on the various agents of different mycoses. The volume is an excellent place of reference and is well written throughout. Their approach is to cater for the student of the field, rather than serve as a laboratory manual and is only let down a little in not looking too far forward to a new era of molecular medicine. The illustrations are packed together and not evenly distributed throughout the areas of study, which unbalances the feel of the volume. These are minor points however – this is a very useful volume indeed to have in the library or on the laboratory reference shelf.

■ ***Neil Gow***
University of Aberdeen

Emerging Pathogens: The Archaeology, Ecology and Evolution of Infectious Disease

Edited by C.L. Greenblatt & M. Spigelman
Published by Oxford University Press (2003)
H/B £75.00, P/B £35.00, pp. 250
ISBN: H/B 0-19-850900-6, P/B 0-19-850901-4

This book is an attempt to illustrate the connections between the problems of new and emerging pathogens and what can be learned from the study of ancient infections, a field which has only become possible relatively recently due to the introduction of techniques like PCR. Central to understanding the past patterns of infection in human populations are the development of methods for paleomicrobiology and epidemiology. Part of the book focuses on some of these, including molecular taphonomy (the study of the fate of biological material after death), 'ancient' DNA and its use to identify disease, and the use of skeletons to diagnose disease states from bone. I found this a fascinating book, and it succeeds quite well in bringing together a rather diverse set of approaches that are not often considered the business of 'mainstream' microbiology. It will appeal to final year microbiology undergraduates and postgraduates as well as senior researchers in bioarchaeology.

■ ***Dave Kelly***
University of Sheffield

Poisonous Plants and Related Toxins

Edited by T. Acamovic, C.S. Stewart & T.W. Pennycott
Published by CABI Publishing (2003)
£75.00/US$140.00, pp. 608
ISBN: 0-85199-614-0

This book contains 86 of the papers presented at the Sixth International Symposium of Poisonous Plants held in Glasgow in 2001. Although predominantly concerned with poisonous plants and their impact on animal husbandry, nearly 25% have a microbiological topic. Not only is a range of microbial toxins dealt with (mycotoxins from fungi, complex toxins of cyanobacteria and the corynetoxins of *Rathayibacter toxicus*), but also some intriguing interactions between micro-organisms and plants. Thus, swainsonine, an important plant toxin, also produced by several fungi, may interact with the action of *E. coli* Shiga toxin and there may be a correlation in its production by plants such as *Oxytropus lambertii*, and the presence of an endophytic species of *Alternaria*. It is a pity that the Editors did not structure the book into sections, bringing papers on related topics together, and the index is both incomplete and full of errors. Even so, this is a book packed with information and, as each chapter has a detailed bibliography, it provides a useful source book into the literature on plant and microbial toxins with particular reference to animal health. A book for the institutional library rather than the personal bookshelf.

■ ***Maurice O. Moss***
Shalford, Guildford

Molecular Diagnosis of Infectious Diseases, Second Edition. Methods in Molecular Medicine, Vol. 94

Edited by J. Decker & U. Reischl
Published by Humana Press (2004)
US$125.00, pp. 480
ISBN: 1-58829-221-5

This is an excellent text on protein-based diagnosis of infectious diseases, although this is not really clear from its title and so it could potentially be overlooked. A typical and now classical format for chapters is to briefly introduce the topic, describe methods in detail, include a section on helpful tips, called 'Notes', and conclude with references. The book primarily focuses on recombinant proteins and serodiagnosis and there are particularly interesting and useful chapters on Molecular diagnostic resources on the internet and Basic problems of serological laboratory diagnosis. The text is nicely laid out with plenty of figures, although in some, the clarity could be improved. All relevant institutions should have a copy and if you are seeking an up-to-date methodological overview of this field, I would highly recommend it.

■ ***Adrian Eley***
University of Sheffield

Antibody Engineering: Methods and Protocols. Methods in Molecular Biology Volume 248

Edited by B.K.C. Lo
Published by Humana Press (2004)
US$125.00, pp. 576
ISBN: 1-58829-092-1

This new practical contribution to antibody engineering provides a broad and fairly complete series of protocols for the selection, modification, expression and use of antibodies and antibody fragments for research scientists. The book includes versions of well established protocols from earlier manuals, but extends sections which have come to the fore recently. There are particularly useful bioinformatics protocols for the use of databases and structural and conformational analysis. An extended general overview of roles for antibodies in proteomics and genomics is included. This complements a series of specific protocols for physical analysis of antibody–antigen interactions which are important for proteomic exploitation, including the interactive use of bioinformatics and mass spectrometry.
The book presents protocols clearly in stepwise fashion in a style suitable for postgraduate researchers with appropriate training and familiarity with laboratory techniques and jargon, and will be a valuable addition to in-lab books.

■ ***Bill Harris***
University of Aberdeen

Advances in Pectins and Pectinase Research

Edited by F. Voragen, H. Schols & R. Visser
Published by Kluwer Academic (2003)
£91.50/Euro145.00/US$142.00, pp. 504
ISBN: 1-4020-1144-X

This wide-ranging and comprehensive symposium volume assembles a very strong group of researchers in the field of pectins and the enzyme systems that degrade them. The volume contains 36 contributions with major sections on pectin biosynthesis; structure and physical and chemical properties of pectins; molecular genetics and regulation of pectinases; identification, action and three-dimensional structure of pectinases; applications of pectinases in food, feed and novel areas; and recent developments in pectin manufacture and application. As this is a symposium volume it contains articles detailing the latest research findings in the field. It is, therefore, most suitable for institutional purchase or purchase by research groups or individual research scientists requiring a state-of-the-art overview of recent developments in the

properties of these complex carbohydrate molecules and the applications of pectinase enzymes.

■ ***Bob Rastall***
University of Reading

Medical Microbiology, Third Edition

By C. Mims, H.M. Dockrell, R.V. Goering, I. Roitt, D. Wakelin & M. Zuckerman
Published by Mosby/Elsevier (2003)
£35.99, pp. 660
ISBN: 0-7234-3259-7

The third edition of this popular textbook has been updated and expanded. It is concise with clear texts and lots of colourful diagrams and photos. The layout follows a logical progression from host defences through to infections by body system and diagnosis and control. Cross-referencing is good throughout the book; however, due to the broad spectrum of subjects covered, the chapters sometimes lack detail. For more information the chapters refer to the appendix, but the promised extra information is a bit disappointing. The book is clearly clinically based and so are the questions (often case studies) at the end of each chapter. I think it is a great read for medical students and possibly useful on the more basic microbiology undergraduate courses. The book offers good value for money for the individual and will be a valuable resource in any university library.

■ ***Marian Blokpoel***
Imperial College London

Origins of Molecular Biology: A Tribute to Jacques Monod. Revised Edition

Edited by A. Ullman
Published by American Society for Microbiology (2003)
US$49.95, pp. 358
ISBN: 1-55581-281-3

Jacques Monod was a larger than life character (a mountain climber, a hero of the WWII French Resistance and a brilliant cellist) who catalysed huge changes in our knowledge of how genes are expressed and their activity regulated. Many of these changes were based on experiments planned or carried out with others. This book is a collection of essays written by these friends and colleagues, including a galaxy of famous scientists, about Monod's life and science. Contributors range from technical assistants at the Pasteur Institute to senior figures such as François Jacob and Francis Crick. The topics range from how his laboratory ran and the fun experienced by visitors to the Paris lab, to memories of key experiments such as Arthur Pardee's description of the PaJaMa (Pardee–Jacob–Monod) experiment. The editing by Agnes Ullman puts everything into context, creating a marvellous resource for those with an interest in how science happened in the past. Hugely enjoyable and readable.

■ ***Chris Thomas***
University of Birmingham

The Mycota: A Comprehensive Treatise on Fungi as Experimental Systems for Basic and Applied Research, Vol. XII Human Fungal Pathogens

Edited by K. Esser & J.W. Bennett (Volume Editors J. E. Domer & G. S. Kobayashi)
Published by Springer (2004)
Euro169.95/CHF275.00/£130.50/US$189.00, pp. 376
ISBN: 3-540-42629-9

The study of human pathogenic fungi is a small but important area of research. Given the increasing interest in medically important fungi, this volume fills a gap in addressing the molecular basis of the interaction between human pathogenic fungi and their hosts. An impressive list of international authors have written chapters which include detailed coverage of the wide range of molecular techniques used to study epidemiology, pathogenesis and human/pathogen interactions. Emphasis is given as to an understanding of these which can be used for the development of appropriate control strategies. The final section deals with the most recent developments in drug treatment. Each topic is supported with a full, comprehensive and invaluable bibliography. This volume should be an essential acquisition for mycologists and institutions working on medically important fungi, although its cost may be off-putting for individual researchers.

■ ***Alistair R. McCracken***
Queen's University Belfast

Ebola and Marburg Viruses: Molecular and Cellular Biology

Edited by H.-D. Klenk & H. Feldmann
Published by Horizon Bioscience (2004)
£90.00/US$180.00, pp. 370
ISBN: 0-9545232-3-7

This is a fascinating update on the molecular biology, pathogenesis and immunology of viruses of the Filoviridae family. These African viruses may emerge in non-endemic regions of the world at any time, due to increasing global migration, travel and trade, and are also of considerable concern as potential bioterrorism agents. Modern cDNA technology has allowed the accumulation of a vast amount of molecular data without handling the infectious virus (a physical containment category IV micro-organism). Ebola virus has recently been produced from infectious cDNA clones (reverse genetics), and this approach has started to yield exact results on molecular determinants of various viral and pathological phenotypes. The Editors have done a marvellous job in collating up-to-date reviews (references up to 2003) by leading research groups in the field. The book is expensive, but of outstanding value. It is highly recommended to all virologists and infectious disease physicians as well as to molecular biologists, immunologists and interested vaccinologists.

■ ***Ulrich Desselberger***
CNRS, Gif-sur-Yvette

Microbial Biotechnology: Principles and Applications

Edited by L.Y. Kun
Published by World Scientific Publishing (UK) Ltd (2003)
£36.00, pp. 724
ISBN: 981-238-323-9

This book covers a wide range of subject areas from bioinformatics to biopharmaceuticals. The content is relevant and up-to-date, supported by a useful reading list at the end of each chapter. It has mostly achieved its aim to fill a gap in the undergraduate textbook market by focusing on the applications of the microbial biotechnological principles. What is lacking is consistency of style. Some chapters contain a list of useful websites and working problems, others contain one of the two or neither. As for the two other ambitious claims by the publisher and Editor: this book will be a useful reference for postgraduate students at the beginning of their research and possibly may have some use for corporate planners and managers. This is a good source book, it deserves sharper editing and the publisher should focus on the needs of its primary audience.

■ ***Diane Purchase***
Middlesex University

1. Handbook of Fungal Biotechnology, Second Edition. Mycology Series, Vol. 20

2. Fungal Biotechnology in Agricultural, Food, and Environmental Applications. Mycology Series, Vol. 21

Edited by D.K. Arora
Published by Marcel Dekker Inc (2004)
Vol. 20: US$225.00, pp. 592, ISBN: 0-8247-4018-1
Vol. 21: US$195.00, pp. 509, ISBN: 0-8247-4770-4

The *Mycology Series* continues with a second edition of a favourite, *Handbook of Fungal Biotechnology*, and a new volume on *Fungal Biotechnology in Agricultural, Food and Environmental Applications*. The *Handbook* differs from the other volume by including a section on basic methodologies, but there is inevitable overlap. For example, the *Handbook* includes chapters on fungal enzymes, solid-state fermentation, and production of lipids and carotenoids. Both volumes cover aflatoxins and other mycotoxins. So, neither volume is the definitive treatise on fungal biotechnology. There is mention throughout of fungal genomics, but the discussion is rather methodological because the outputs from genomics are only just beginning to be published. It was disappointing that one chapter on genome sequence patterns devoted considerable space to recognition of matrix attachment regions (MARs) without citing the one published paper on fungal MARs (Belshaw *et al.*, 1997, *Mol Gen Genet* 256, 18–27). Despite drawbacks, I am pleased to have both volumes available as easily accessed and comprehensive reference sources.

■ ***David Archer***
University of Nottingham

Books received

Peptide Nucleic Acids: Protocols and Applications, Second Edition

Edited by P.E. Nielsen
Published by Horizon Scientific Press (2003)
£90.00/US$180.00, pp. 318
ISBN: 0-9545232-4-5

Diary

july 04

MICROBIAL FERMENTATION AND MAMMALIAN CELL CULTURE: INDUSTRIAL AND REGULATORY ISSUES AND SOLUTIONS

De Vere Cavendish Hotel, London 8 & 9 July 2004

CONTACT: Management Forum Ltd, 48 Woodbridge Road, Guildford GU1 4RJ (Fax 01483 536424; email registrations@management-forum.co.uk; www.management-forum.co.uk)

7TH INTERNATIONAL MAREK'S DISEASE SYMPOSIUM

St Catherine's College, Oxford 10–14 July 2004

CONTACT: Dr Margaret M. Carr, Institute for Animal Health, Compton, Newbury RG20 7NN (Tel. 01635 577227; Fax 01635 577303; email margaret.carr@bbsrc.ac.uk; www.iah.bbsrc.ac.uk/mdc)

23RD ANNUAL SCIENTIFIC MEETING OF THE AMERICAN SOCIETY FOR VIROLOGY (SPONSORED BY MCGILL UNIVERSITY, MONTREAL)

Montréal, Québec, Canada 10–14 July 2004

CONTACT: Sidney Grossberg, Secretary–Treasurer, American Society for Virology, Dept of Microbiology and Molecular Genetics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226-0509, USA (Tel. +1 414 456 8104; Fax +1 414 456 6566; email ASV@mcw.edu; www.mcw.edu/asv)

BIOSCIENCE2004: FROM MOLECULES TO ORGANISMS

SECC, Glasgow 18–22 July 2004

CONTACT: Meetings Office, Biochemical Society, 59 Portland Place, London W1B 1QW (Tel. 020 7580 3481; Fax 020 7637 7626; email info@BioScience2004.org; www.BioScience2004.org)

ANAEROBE 2004: 7TH BIENNIAL CONGRESS OF THE ANAEROBE SOCIETY OF THE AMERICAS

Annapolis, Maryland, USA 19–21 July 2004

CONTACT: Anaerobe Society of the Americas, PO Box 452058, Los Angeles, CA 90045-8526, USA (Tel. +1 310 216 9265; Fax +1 310 216 9274; email asa@anaerobe.org; www.anaerobe.org)

PRE-MEETING WORKSHOP: RAPID DEDUCTION OF BACTERIA STRESS RESPONSE PATHWAYS: GENOMICS, PROTEOMICS, METABOLICS AND BIOINFORMATICS (SIM ANNUAL MEETING)

Anaheim Marriott, Anaheim, California, USA 25 July 2004

CONTACT: SIM, 3929 Old Lee Highway, Suite 92A, Fairfax, VA 22030-2421, USA (Tel. +1 703 691 3357; Fax +1 703 691 7991; email info@simhq.org; www.simhq.org)

INDUSTRIAL MICROBIOLOGY AND BIOTECHNOLOGY MEETING. (SIM ANNUAL MEETING)

Anaheim Marriott, Anaheim, California, USA 25–29 July 2004

CONTACT: SIM (*see above*)

INTERNATIONAL SYMPOSIUM. THREAT OF INFECTION. MICROBES OF HIGH PATHOGENIC POTENTIAL. STRATEGIES FOR DETECTION, CONTROL AND ERADICATION

Würzburg, Germany 25–28 July 2004

CONTACT: Mrs Claudia Borde, Institut für Molekulare Infektionsbiologie, Röntgenring 11, D-97070 Würzburg, Germany (Tel. +49 931 312575; Fax +49 931 312578; email claudia.borde@mail.uni-wuerzburg.de; www.uni-wuerzburg.de/infektionsbiologie/leopoldina.htm)

august 04

10TH INTERNATIONAL SYMPOSIUM ON MICROBIAL ECOLOGY (ISME). MICROBIAL PLANET: SUB-SURFACE TO SPACE

Cancun, Mexico 22–27 August 2004

CONTACT: Prof. H.M. Lappin-Scott (email h.m.lappin-scott@ex.ac.uk; www.kenes.com/isme)

aug–sept 04

BIOCAT 2004

University of Technology, Hamburg, Germany 29 August–1 September 2004

CONTACT: Ms Gerlinde Loebkens, TUHH-Technologie GmbH, Harburger Schloßstr. 6-12, 21079 Hamburg, Germany (Tel. +49 40 76618012; Fax +49 40 76618018; email loebkens@tutech.de; www.biocat2004.de)

september 04

ALTERNATIVE AND CONVENTIONAL ANTI-FOULING STRATEGIES. INTERNATIONAL CONFERENCE OF THE BIODETERIORATION AND BIODEGRADATION SOCIETY

Aquatorium, Mülheim, Germany 13–15 September 2004

CONTACT: Prof. Dr Hans-Curt Flemming, Secretariat Ingelore Pinders, IWW, Moritzstr. 26, D-45476 Mülheim, Germany (Tel. +49 208 40303401; email HansCurtFlemming@compuserve.com *or* i.pinders@iww-online.de; www.iww-online.de)

BMS ANNUAL SCIENTIFIC MEETING: FUNGI IN THE ENVIRONMENT

Nottingham 13–15 September 2004

CONTACT: BMS Meetings Manager (email john.peberdy@nottingham.ac.uk; www.britmycolsoc.org.uk)

HEALTH PROTECTION AGENCY ANNUAL CONFERENCE 2004

University of Warwick 13–15 September 2004

CONTACT: email hpaconference@hpa.org.uk (www.hpaconference.org.uk)

11TH BIENNIAL CHALLENGER CONFERENCE FOR MARINE SCIENCE 2004

Liverpool 13–17 September 2004

CONTACT: Dr Judith Wolf, Proudman Oceanographic Laboratory, Bidston Observatory, Prenton, CH43 7RA (Tel. 0151 653 8633; Fax 0151 653 6269; email jaw@pol.ac.uk; www.pol.ac.uk/ms2004/)

NSF INTERNATIONAL COURSE – WATERBORNE PATHOGENS: MINIMIZING RISK ASSOCIATED WITH BUILDING WATER SYSTEMS (IN CONJUNCTION WITH HC INFORMATION RESOURCES INC.)

NSF Headquarters, Ann Arbor, Michigan, USA 14 September 2004

CONTACT: Tel. +1 800 673 6275 (www.nsf.org/cphe)

ACINETOBACTER 2004: 6TH INTERNATIONAL SYMPOSIUM ON THE BIOLOGY OF *ACINETOBACTER*

Dublin, Ireland 15–17 September 2004

CONTACT: Kevin Towner, Department of Microbiology, University Hospital, Nottingham NG7 2UH (Tel. 0115 970 9163; Fax 0115 942 2190; email Kevin.Towner@mail.qmcuh-tr.trent.nhs.uk)

EURESCO CONFERENCE – CELLULAR AND MOLECULAR BASIS OF REGENERATION

San Feliu de Guixols, Spain 18–23 September 2004

Contact: Corinne Le Moal, Publicity Officer & Conference Organiser, EURESCO Office, 1 quai Lezay-Marnésia, 67080 Strasbourg, France (Tel. +33 388 767 135; Fax +33 388 366 987; email clemoal@esf.org; www.esf.org/ euresco/04/lc04177)

JPGM GOLD CON: 50 YEARS OF MEDICAL WRITING – INTERNATIONAL CONFERENCE ON JOURNAL WRITING AND PUBLISHING

Mumbai, India 23–26 September 2004

CONTACT: Dr Atul Goel, Dept of Neurosurgery, Seth G.S. Medical College, Parel, Mumbai-400 012, India (Tel. +91 22 24129884; Fax +91 22 25032398; email goldcon@jpgmonline.com; www.jpgmonline.com/goldcon.asp)

october 04

XIII BOTRYTIS SYMPOSIUM

Antalya, Turkey 25–31 October 2004

CONTACT: Dr Yigal Elad (email elady@volcani.agri.gov.net.il; www.agri.gov.il/events/BotrytisSym/BotrytisSymposium.pdf)

november 04

GENETICS AND MOLECULAR BIOLOGY OF INDUSTRIAL MICROORGANISMS/ BIOTECHNOLOGY OF MICROBIAL PRODUCTS (GMBIM/BMP)

Hilton San Diego Resort, San Diego, California, USA 14–18 November 2004

CONTACT: SIM (*see above*)

Comment

Cold rush for drugs?

A wide variety of microbes lives in the icy wastes of Antarctica. Nick Russell believes that exploiting their commercial applications may not be in the interests of protecting this unique environment.

The early days of antibiotic and drug discovery were typified by the screening of soil bacteria as a primary search tool. Nowadays, a novel therapeutic agent is much more likely to be a chemical derivative of an existing compound or one that has been synthesized on the basis of computerized modelling of structure–activity relationships. In addition, the search has turned to more unusual sources, ranging from rare plants to micro-organisms that live in extreme environments, so-called extremophiles.

The initial focus of this new 'extreme biotechnology' was initially on thermophiles. However, it is generally recognized that, although thermophiles have provided very important thermostable polymerase enzymes for PCR (fundamental to most biotechnology), they have not fulfilled their promise in the broader sense of supplying new biotechnological tools.

ABOVE:
Mount Melbourne viewed across sea-ice in Wood Bay, Antarctica. Psychrophiles can be isolated from the ice, water and soil, and thermophiles from thermal vents near the top of this volcanic mountain, demonstrating the diversity of habitats and micro-organisms in this region.
COURTESY N. RUSSELL

At the other end of the scale, psychrophiles that live in cold, even frozen habitats such as tundra and sea-ice have been investigated for their biotechnological potential. These cold-adapted bacteria and their enzymes, which function at temperatures as low as –20 °C have applications in a wide range of industrial applications from keeping ice-cream soft and cold-water washing to environmental biosensors and new drug discovery. The biodiversity of severely cold habitats is more diverse than first predicted and they contain new species with novel properties. For example, marine Antarctic bacteria have been considered as the source of dietary supplements, because their membrane lipids contain the same polyunsaturated fatty acids that are precursors of bioactive molecules such as prostaglandins found in mammals.

Although there are many cold habitats on Earth, it is Antarctica that continues to capture the imagination and to be the focus of research on 'cold biotechnology'. Fresh attention has been drawn to the biotechnological exploitation of Antarctic psychrophiles and their cold-active enzymes with the recent publication of a follow-up study to a 2003 report from the United Nations University, Institute of Advanced Studies UNU/ IAS. The initial report dealt with several issues of biodiplomacy, including as a specific topic '*The International Regime for Bioprospecting. Existing Policies and Emerging Issues for Antarctica*'. The follow-up study, based on interviews with representatives from industry, academia and national Antarctic organizations, has highlighted the inadequacy of current legislation and international organization for the protection of the natural resources of Antarctica. Ownership of intellectual property (e.g. bacterial culture collections, isolated enzymes) usually lies with the institution that collected the samples, and industry has not been much engaged in Antarctic research – a situation that does little to help scientists in their search for financial support.

So why the concern?

The Antarctic Treaty states clearly the principles of freedom of scientific investigation and access, that the results of scientific research should be freely available, and that living resources should be conserved, but it does not deal specifically with commercial exploitation. The Treaty's advisory body, the Scientific Committee on Antarctic Research, has raised the concern that bioprospecting should not put pressure on resources in such a delicately balanced ecosystem. Scientists and governments have concerns that individual patents may compromise the free advance of understanding and the concept of Antarctica as a continent free of national constraints. Regulations to control bioprospecting will need to be discussed and agreed upon by all those countries with jurisdiction over administering the various sectors of Antarctica. This will take time, and time has a habit of running out. The first full genomic sequences of Antarctic bacteria are now appearing and will stimulate biotechnological research of psychrophiles and interest in bioprospecting in Antarctica. Now is the time to act and for governments, industry and scientists to show that they can co-operate on an international scale in drawing up regulations to establish how the biotechnological resources of this continent can be harnessed within the principles of the Antarctic treaty and without compromising the proper exploitation of such a valuable biotechnological resource.

The full report on bioprospecting in Antarctica is available online at ***www.ias.unu.edu/binaries/UNUIAS_AntarcticaReport.pdf****. The Antarctic Treaty and related information can be accessed at www.scar.org/Treaty*

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● Please note that views expressed in *Comment* do not necessarily reflect official policy of the SGM Council.