

# Antibiotics Chemotherapy



DECEMBER 2002  
VOLUME 6  
NUMBER 3

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## The future in systemic therapy of cancer

The standard treatments for cancer in the past 25 years have included surgery, radiation therapy and single agent or combination chemotherapy. Much progress has been made with improvements in diagnosis, staging and all modalities of therapy. With our improved knowledge of genes, we are now able to identify patients at high risk of developing certain types of cancer, which, frequently, is much more accurate than just using family history of, for example, breast cancer. Prophylactic surgery (mastectomy or oophorectomy) in the case of breast cancer in patients at high risk (with BRCA1 and BRCA2) has already revealed potential patient benefits, although there are still major ethical issues surrounding the use of genetic testing in these patients that need to be resolved.

### 'Targeted therapy'

A major change in systemic therapy has been the use of 'targeted therapy' for a variety of haematological malignancies and solid tumours. This brings us into a period of great excitement with the development of new oral and parenteral therapies developed for specific targets, not necessarily specific cancers. Some already available marketed or experimental agents include: ras/raf inhibitors such as farnesyl transferase inhibitors (R115777 and SCH66336); inhibitors of protein kinase C-alpha (antisense oligonucleotides by ISIS, especially ISIS 3521 [LY10009 - Eli Lilly]) which is



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Budapest – venue for the first ISC Disease Management Series meeting.

being used in lung cancer; COX-2 inhibitors that may spontaneously get rid of polyps with malignant potential in the colon and are also being used with chemotherapy in other malignancies; and tyrosine kinase inhibitors, such as those that act on epidermal growth factor receptors (EGFR). Over-expression of the target only occurs in certain tumours yet may not be required for the agent to work. Many drugs have multiple effects, whereas others are very specific and only work if the target is over-expressed. An example of the latter is trastuzumab (Herceptin® - Roche), approved by the US Food and Drug Administration for metastatic breast cancer which targets the extracellular domain of the human EGFR 2 protein, HER2.

### EGFR inhibitors

There are a variety of EGFR inhibitors available, working at different points of a very complicated pathway. A large number of clinical trials are either under way or completed with these agents in a number of tumour types, with

non-small-cell lung cancer (NSCLC) being one of the most well studied to date. The agents studied include: Cetuximab-C225 by ImClone, which is a monoclonal antibody that binds to the extracellular domain of EGFR; oral tyrosine kinase inhibitors including, among others: gefitinib (Iressa™ - AstraZeneca), erlotinib (Tarceva™ - Genentech) and CI-1033 (pan-erb tyrosine kinase inhibitor - Pfizer).

Some of the oral agents show activity as single agents in NSCLC, even in those pre-treated with more than two types of chemotherapy. Tarceva™ is being compared to placebo, while Iressa™ has been studied in a two-dose comparison in a large number of patients. Responses and symptom relief and improvement in quality of life have been seen, but survival data are not available to date. Tarceva™ and Iressa™ cause diarrhoea and fairly severe skin toxicity, both rarely seen with chemotherapy, making it reasonable to try to combine

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*Antibiotics Chemotherapy* is the official newsletter of the International Society of Chemotherapy. Distribution is made possible by educational grants and this issue has received generous support from:



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West Sussex BN11 1DJ, UK.  
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*Antibiotics Chemotherapy*, ISSN 1469-199X, is produced on behalf of the ISC by Cambridge Medical Publications, a division of PAREXEL MMS Europe Ltd, Wicker House, High Street, Worthing, West Sussex BN11 1DJ, UK.  
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# Upgrading biodefense

'Biodefense' means the efforts made to defend against potential biological agents used by terrorists. It is significant that the term was not in our vocabulary a year ago; today, it is a subject receiving increasing attention from government agencies.

The mailing of letters containing *Bacillus anthracis* spores in the USA in the past year, coupled with the documented efforts made by Iraq in preparation for biological warfare,<sup>1</sup> and the evidence of increased terrorist activity seen by the events of September 11, 2001 in the USA, have focused attention on how a nation can best defend itself against biological attacks.

Various agencies in the USA have particularly prioritized this issue. The Centers for Disease Control and Prevention (CDC) has established a list of potential biological agents that pose a risk to national security, categorizing them according to importance/level of risk (Table 1).<sup>2</sup> The National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health has also established its own priority list of these agents.<sup>3</sup>

**Table 1: Biological agents categorized according to importance/risk level (CDC)<sup>2</sup>**

### Category A

*Bacillus anthracis* (anthrax)  
*Clostridium botulinum* toxin  
*Yersinia pestis* (plague)  
*Variola major* (smallpox)  
*Francisella tularensis* (tularemia)  
 Viral haemorrhagic fevers (Ebola, Marburg, Lassa, Machupo viruses)

### Category B

*Brucella* species  
*Clostridium perfringens* epsilon toxin  
*Burkholderia mallei*; *B. pseudomallei*  
*Chlamydia psittaci*; *Coxiella burnetii*  
*Ricinus communis* toxin  
 Staphylococcal enterotoxin B  
*Rickettsia prowazekii*  
 Viral encephalitis  
 Water safety threats  
 Food safety threats

### Category C

Nipah virus; hantavirus

## Biodefense research

The NIAID, through the use of a select panel of experts, has established a strategic plan for biodefense research that outlines research needs in the broad area of bioterrorism and emerging and re-emerging infectious diseases, focusing particularly on the biology of the microbe, the host response, and the basic and applied research aimed at the development of diagnostics, therapeutics and vaccines against these agents.<sup>4</sup> Research resources, facilities and scientific manpower needed to conduct such research were also addressed by the panel.

A significant increase in funding, over US\$1 billion, is in the process of being provided to the NIAID in support of biodefense research. Much of this has been allotted to the establishment of a Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs) Program, and to the construction of Regional Biocontainment Laboratories (RBLs) and National Biocontainment Laboratories (NBLs). It is understood that the RCEs, planned for development in 10 regions in the USA, will:

- Develop investigator-directed research;
  - Train researchers and other personnel for biodefense research activities;
  - Develop translational research capacity to test and validate vaccine, therapeutic and diagnostic concepts for emerging infectious diseases, including agents of bioterrorism;
  - Develop and maintain comprehensive core facilities for investigators from academia and the private sector for the performance of experiments and for the testing and evaluation of vaccines, therapies and diagnostics for the biological agents prioritized by the CDC and the NIAID.
- The RCEs will also prepare and



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*Protective clothing offers protection against anthrax and other potential biological agents.*

make available facilities and scientific support for first-line responders in the event of a national biodefense emergency. Visit the website (<http://grants1.nih.gov/grants/guide/rfa-files/RFA-AI-02-031.html>) for more information on these centres and how to apply for funding. The RBLs are planned for construction in the same regions in the USA that will be used for the RCEs. They will be Biosafety Level (BSL) 2 and 3 facilities. Plans are to construct one or two NBLs, which will include BSL-4 biocontainment capabilities, including animal facilities, to allow research on the most dangerous biological agents. Clinical isolation units for treatment of patients and the conducting of human trials of virus-based vaccines will also be included. Establishment of these new laboratories will significantly increase the number of BSL-3 and -4 facilities in the country. Further information on the RBL/NBL program can be found on the NIAID website (<http://www.niaid.nih.gov/cgi-shl/cmb/rfps.cfm>). The NIAID has indicated that it plans to rapidly review and approve proposals for RCEs and RBLs.

It is obvious that those involved in public health, along with the political powers, in the

USA are making a major commitment to the biodefense issue. It is hoped other nations will also step forward to further efforts worldwide in this increasingly important health arena. ■

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## The history of antibiotics: the Japanese story\*

In 1948 Japan became the third country, after the USA and UK, to become self-sufficient in penicillin manufacture. Over 117 useful antibiotics and related agents have originated from Japan, of which 41 have been licensed globally.

### The dawn of research (1944–1949)

Japanese antibiotic research began with penicillin production between 1944 and 1945, when Professor Hamao Umezawa's research group produced 'HEKISO', so called because of its blue colour.

After the Second World War, the Japan Penicillin Research Association (later called the Japan Antibiotics Research Association [JARA]) was established to unite experts in microbiology, fermentation, natural product chemistry, organic chemistry, biology and physics in the manufacture of penicillin preparations, and those in pharmacy and medicine who applied these preparations to treat various infectious diseases. Penicillin production began in 1946 under the direction of JARA (guided by American scientists including Professor Jackson W Foster). The clinical division of JARA later became independent and formed the Japanese Society of Chemotherapy (JSC) in 1953, chaired by Professor Kanshi Sasa.

In 1946, Japan produced 47 million units of penicillin (an amorphous mixture of F, G, X and K), becoming self-sufficient when 297 billion units of penicillin G were produced in 1948, and exporting this antibiotic to Korea and China in 1949. Penicillin G production increased constantly thereafter, reaching 57 trillion units in 1954 (enough to treat 2.4 million patients at a daily dosage of 2.4 million units for

10 days), when 83 pharmaceutical companies were involved in its manufacture and supply.

In 1949 the Umezawa group discovered the first novel antibiotic, fradiomycin, in the fermentation broth of *Streptomyces fradiae*. Fradiomycin was later shown to be identical to neomycin, also identified by Professor Selman A Waksman (USA) in 1949: neomycin was not approved in Japan and fradiomycin was not licensed abroad. The Umezawa group also discovered the first antifungal antibiotic in the world, aureothricin, in 1949, although it was only licensed in Japan.

### The golden era – new antibiotics of microbial origin (1950–1965)

In 1950, three clinically important antibiotics – chlortetracycline, chloramphenicol and streptomycin – were introduced into Japan from the USA; the 14-membered macrolide antibiotic, erythromycin, followed in 1953. These antibiotics showed different therapeutic activities, which stimulated Japanese exploratory research in microbial products.

Colistin, a peptide antibiotic, was discovered by Dr Yasuo Koyama (Lion Antibiotics Co.) in 1950, and was the first Japanese antibiotic to be used worldwide. Colistin is still used to treat Gram-negative bacterial infections including those caused by *Pseudomonas aeruginosa*. A methansulphonate derivative of colistin (colistimethate in the USA) has also been used widely. Another peptide antibiotic, gramicidin J (gramicidin S in Russia), was discovered by Professor Shohei Otani's group at Osaka City University in 1952; this was



Joichi Kumazawa.

only used in Japan, as a topical agent. The mikamycins, discovered in 1956 by Professor Hiroshi Yonehara's group, possess a depsipeptide structure similar to the virginiamycins and pristinamycins discovered in the USA in 1955 and France in 1962, respectively. Although the mikamycins had limited use domestically as topical preparations, they have received recent attention and a mixture of pristinamycin derivatives (under the name of Synercid®) has been developed to treat infections caused by vancomycin-resistant enterococci (VRE).

A 16-membered macrolide antibiotic, leucomycin complex (now called kitasamycin), was identified by Professor Toju Hata's group in 1953. During development of a paediatric form of kitasamycin, an acetylated derivative which had no bitter taste was prepared (acetylkiasamycin). A 16-membered macrolide antibiotic, spiramycin was introduced from France in 1963 and was modified to improve its pharmacokinetic properties. As a result, acetylspiramycin, with improved metabolic stability, was synthesized by the Kyowa Hakko Kogyo Co. in 1965 and introduced into clinical use. Extensive studies with 16-membered macrolide antibiotics led to the discovery of other antibiotics within this class that are now used widely in Europe – josamycin and



Morimasa Yagisawa.

josamycin propionate (1967, Yamanouchi Pharmaceutical Co.) and midecamycin (1971, Meiji Seika Kaisha).

The discovery of kanamycin by the Umezawa group in 1957 was a significant event. This agent has excellent activity against infections caused by penicillin-resistant *Staphylococcus aureus*, streptomycin-resistant *Mycobacterium tuberculosis* and chloramphenicol-resistant *Shigella* strains. Kanamycin was produced by fermentation along with two structurally related analogues, one of them, bekanamycin (originally named kanamycin B), showing stronger activity than kanamycin.

Trichomycin (renamed hachimycin), a heptaene antifungal antibiotic, was discovered by Professor Syogo Hosoya in 1952. This discovery came 2 years after the tetraene antibiotic nystatin was identified in the USA, but 4 years before the most important heptaene antibiotic, amphotericin B, was discovered. In subsequent research on antifungal agents, variotin (renamed pecilocin by the World Health Organization) was identified by Professor Yusuke Sumiki's group at the University of Tokyo in 1951, followed by pentamycin (1958, Professor Sumio Umezawa), azalomycin F (1960, Dr Mamoru Arai's group), siccanin (1961, Sankyo Co.) and pyrrolnitrin (1965, Professor Kei Arima's group). Their usage has been

\*Presented at the 22nd International Congress of Chemotherapy, Amsterdam, The Netherlands, 3 July 2001, and adapted with permission from the *Journal of Infection and Chemotherapy* (J Infect Chemother 2002; 8: 125–133).

limited to topical treatments for athlete's foot and candidiasis in Japan.

The first antibiotic found to have anticancer activity, sarkomycin, was discovered by the Umezawa group in 1953 after it was administered experimentally to animals with cancers. Structural and synthetic studies on sarkomycin were conducted by Bristol-Myers in the USA. Mitomycin C, was identified in 1955 by the Hata group following the discovery of carzinophilin in 1954, and was introduced globally in the 1970s, remaining the drug of choice in treatment of certain cancers. Chromomycin A<sub>3</sub> was discovered by Dr Suetatsuoka's group (1955, Takeda Chemical Industries) and was later shown to possess a similar structure to mithramycin (discovered in 1962 and used in the USA).

The first natural compound possessing anticancer activity was the actinomycin C complex, discovered in 1949 by the Bayer group and initially considered to be an antimicrobial agent, although its anticancer activity was identified around 1954. When bleomycin was discovered by the Umezawa group in 1965, its introduction into the world market was a landmark in the chemotherapy of carcinoma and in the elucidation of the biochemical mechanisms of action of anticancer antibiotics. Bleomycin was the first anticancer agent to show specificity of tissue/organ distribution and metabolism, leading to unique therapeutic effects in particular cancers, and distinct adverse reactions. A macromolecular anticancer antibiotic, neocarzinostatin (renamed zinostatin), was discovered by Professor Nakao Ishida's group also in 1965.

Extensive agricultural and veterinary research led to the discovery of blasticidin S (1958) by the Sumiki group, kasugamycin (1965) by the Umezawa group, polyoxin complex (1965) by the group of Dr Saburo Suzuki at the RIKEN Institute for rice plant

protection, and destomycin (1965) by Meiji Seika Kaisha (used as an antihelminthic in pigs).

**Maturation of research in natural and semi-synthetic approaches (1966–1980)**

Synthesis and development of cefazolin by the Fujisawa Pharmaceutical Co. group in 1969 triggered extensive Japanese research into β-lactam antibiotics. Cefazolin remained the first choice among parenteral cephalosporins for 30 years, because of its potent activity against Gram-positive bacteria and Gram-negative pathogens, especially *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus vulgaris*: newer cephalosporins did not supplant cefazolin until 2nd- and 3rd-generation cephem antibiotics emerged. A 2nd-generation cephalosporin, cefotiam (synthesized in 1977, Takeda Chemical) was a prime candidate for worldwide use, but high production costs reduced interest. Two 3rd-generation derivatives have been widely used: cefoperazone, synthesized by Toyama Chemical Co. in 1978 (later introduced worldwide by Lederle) and ceftizoxime (1979, Fujisawa Pharmaceutical).

Of the novel analogues of the cephem nucleus, oxacephamycin had been synthesized and evaluated. Latamoxef (1978, Shionogi & Co.) was marketed in the USA by Eli Lilly under the US-adopted name of moxalactam. Among the cephamycins, cefmetazole (1976, Sankyo) and cefotetan (1979, Yamanouchi Pharmaceutical) were introduced globally by Upjohn and ICI Pharmaceuticals, respectively. Parenteral cepheps used domestically include: ceftazolidime (1971, Chugai Pharmaceutical Co.); cefsulodin and cefmenoxime (1974 and 1978, respectively, Takeda Chemical); cefpiramide (1979, Sumitomo Chemical Co.); cefbuperazone (1979, Toyama Chemical); and cefpimizole (1980, Ajinomoto Co.).

Piperacillin, the semi-synthetic penicillin synthesized

Table: Summary of antibiotics/chemotherapeutics and bioactive microbial products originating from Japan

Category	No. of products discovered (no. exported)					Total
	1946–1955	1956–1965	1966–1975	1976–1985	1986–1995	
β-lactam antibiotics	0 (0)	0 (0)	5 (1)	27 (12)	8 (2)	40 (15)
Aminoglycoside antibiotics	1 (0)	2 (1)	5 (2)	1 (0)	0 (0)	9 (3)
Macrolide antibiotics	2 (0)	1 (0)	4 (2)	3 (1)	0 (0)	10 (3)
Peptide antibiotics	2 (1)	2 (1)	2 (0)	0 (0)	0 (0)	6 (2)
Quinolone antibacterials	0 (0)	0 (0)	2 (0)	7 (4)	3 (3)	12 (7)
Antifungal antibiotics	3 (1)	4 (0)	0 (0)	0 (0)	0 (0)	7 (1)
Anticancer antibiotics	3 (2)	3 (2)	2 (0)	1 (0)	0 (0)	9 (4)
Bioactive microbial products	0 (0)	0 (0)	2 (0)	2 (1)	2 (1)	6 (2)
Agricultural antibiotics	0 (0)	4 (1)	8 (2)	4 (1)	2 (0)	18 (4)
<b>Subtotal</b>	<b>11 (4)</b>	<b>16 (5)</b>	<b>30 (7)</b>	<b>45 (19)</b>	<b>15 (6)</b>	<b>117 (41)</b>

by Toyama Chemical (1976), was shown to possess excellent activity against a wide-range of Gram-positive, Gram-negative and anaerobic bacteria and to have favourable pharmacokinetic properties. Piperacillin was marketed globally by Lederle and remains a first-choice antibiotic. Other penicillin derivatives synthesized in Japan and used domestically include: sulbenicillin (1964, Takeda Chemical), talampicillin (1974, Yamanouchi Pharmaceutical) and aspicillin (1979, Tanebe Seiyaku Co.).

A semi-synthetic approach to obtaining effective derivatives of aminoglycoside antibiotics, to control resistant infections, proved successful. Dibekacin (1971, the Umezawa group) and amikacin (1972, Dr Hiroshi Kawaguchi at Bristol-Banyu Research Institute) were designed and synthesized based on knowledge of biochemical mechanisms of bacterial resistance to aminoglycoside antibiotics such as kanamycin and neomycin. Arbekacin (1973, the Umezawa group), a derivative of dibekacin, has been used extensively in Japan to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

Further research led to the discoveries of aminoglycoside antibiotics, ribostamycin (1970, Meiji Seika Kaisha), and micromycin and astromycin (in 1975 and 1976 respectively, Kyowa Hakko), although these are only used in Japan. A mixed peptide antibiotic, enviomycin, identified by Toyo Jozo Co. in 1971, has potent antimycobacterial activity with lower toxicity than other compounds of the same class, viomycin and capreomycin.

To improve the pharmacological properties of the 16-membered macrolide antibiotics, a semi-synthetic approach was applied. Subsequently, midecamycin acetate and rokitamycin were synthesized in 1976 by Meiji Seika Kaisha and in 1980 by Toyo Jozo Co., respectively, and introduced for clinical use in Japan.

The first of the fluoroquinolone antibacterials, norfloxacin, was synthesized in 1977 by Kyorin Pharmaceutical Co. and marketed globally by Merck Sharp & Dohme. Its invention relied on accumulated knowledge of the structure-activity relationships of non-fluorinated pyridone carboxylic acids, piromidic acid (1971) and

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## Pandemic influenza and the global vaccine supply ~

Presented at the 4th European Congress of Chemotherapy and Infection, Paris, France, May 2002

### David S Fedson



AVENTIS PASTEUR MSD,  
LYON, FRANCE

Dr David S Fedson was appointed Harry T Peters, Jr Professor of Internal Medicine at the University of Virginia School of Medicine in 1988. He became Director of Medical Affairs for Aventis Pasteur MSD, a European vaccine company located in Lyon, France, in 1995. Dr Fedson's research has focused on adult immunization with influenza and pneumococcal vaccines. He served on the Advisory Committee on Immunization Practices and

the National Vaccine Advisory Committee (NVAC) and wrote the NVAC report on Adult Immunization that now guides federal policy in the USA. In 1999 he received the Research Achievement Award in Adult Immunization in the United States given by the Centers for Disease Control and Prevention, the Health Care Financing Administration and the National Coalition on Adult Immunization.

Influenza vaccine use is increasing rapidly. In 2000, more than 230 million doses were used worldwide. Of these doses, approximately one-third were used in countries outside western Europe, North America, Australia and New Zealand, yet 85% of the world's supply of influenza vaccine comes from just nine companies located in developed countries. The threat of pandemic influenza will place an unprecedented burden on these companies to produce enough pandemic vaccine to satisfy global demand.

One approach to increasing the supply of pandemic vaccine would be to increase the

demand for influenza vaccine in interpandemic years. Although this traditional market approach to meeting vaccine demand will be helpful, it will not succeed in meeting the very large increase in demand that will come with a pandemic. Moreover, vaccine companies will face the risk that political leaders in the vaccine-producing countries will prohibit the export of pandemic vaccine until their countries' domestic needs have been met. If this happens, it will be very difficult for many developed and almost all developing countries to obtain adequate supplies of pandemic vaccines.

#### Steps needed to increase vaccine supply

Several suggestions have been made to address the problems of vaccine supply. First, efforts must be made to ensure that pandemic vaccine production can begin as rapidly as possible. This will probably require that 'reverse genetics' be used to produce the vaccine seed strains companies will need. Secondly, the type of vaccine and vaccination schedule that will be needed

must be defined beforehand, recognizing that some or all individuals may need two doses and that an adjuvanted vaccine might be required. Thirdly, a global protocol for registering vaccines produced by any qualified vaccine company must be developed. Fourthly, national recommendations for influenza vaccination in interpandemic years and reimbursement policies must be expanded. Fifthly, the macro- and microepidemiology of influenza vaccination in all countries must be documented, and critical factors associated with high levels of vaccine use defined. Finally, a process for coordinating the international distribution of pandemic vaccine must be created to ensure an equitable distribution of whatever supplies of vaccine are available. This last issue is largely a matter of politics, economics and international law.

The global supply of pandemic vaccine will require the creative efforts of many institutions, most notably the World Health Organization. The work that needs to be done must begin now. ■

## Vancomycin-resistant *Staphylococcus aureus*\*

The first clinical isolate of *Staphylococcus aureus* with reduced susceptibility to vancomycin (minimum inhibitory concentration [MIC] =8 mg/l) was reported by K Hiramatsu of Japan in 1996. Such strains have since been isolated from other parts of the world.

In June 2002, the first case of infection by a vancomycin-resistant *S. aureus* (VRSA; MIC >128 mg/l) was reported in Michigan, USA. The strain was isolated from a catheter-exit site from a patient with diabetes, peripheral vascular disease and chronic renal failure. The patient was on dialysis and had been treated for chronic foot

ulcerations with multiple antibiotics, including vancomycin. The patient developed methicillin-resistant bacteraemia caused by an infected arteriovenous haemodialysis graft, after undergoing amputation of a gangrenous toe. The infected graft was removed and the infection was treated with vancomycin and rifampicin. The patient subsequently developed a catheter-site infection, and the catheter was removed: cultures of the exit site and the catheter tip grew VRSA, vancomycin-resistant enterococci and *Klebsiella*. VRSA was also isolated from a foot ulcer. Cultures from other sites (e.g. healed catheter site, nares)

did not grow VRSA. Aggressive wound care and systemic therapy with trimethoprim/sulphamethoxazole were initiated, and the patient is now clinically stable.

Epidemiological studies did not reveal any VRSA transmission among patients, healthcare workers and other contacts.

The isolate had a *vanA* vancomycin resistance gene similar to that found in enterococci. This suggests that there could have been a transfer of the gene from enterococci as it was also isolated from the same catheter-site swab. Conjugative transfer of *vanA* from enterococci to staphylococci had been demonstrated *in vitro*.<sup>1</sup> The

presence of *mecA* gene responsible for oxacillin-resistance was also detected. The organism was susceptible to other antibiotics such as chloramphenicol, minocycline, tetracycline, trimethoprim/sulphamethoxazole and linezolid. ■

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(\*Adapted from CDC-MMWR Report, July 2002. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5126a1.htm>)

## 5th European Congress of Chemotherapy and Infection



Rhodes, Greece,  
17–20 October 2003

The scientific programme for ECC-5 is currently being developed with three main themes. The programme will be presented by major in-depth symposia, supplemented by expert lectures on major talking points, oral and poster research presentations, and interactive workshops. There will also be a special postgraduate course for trainees held during the Congress.

### THEME 1: Infection in the community

Over 90% of antibiotic use occurs in the home rather than the hospital. The emergence of antibiotic resistance in common community pathogens such as *Streptococcus pneumoniae* and *Escherichia coli* has focused attention on the general use of antibiotics to ensure the most appropriate use. Particular questions are raised concerning when antibiotics should be given and when withheld. Should one delay the use of antibiotics and risk allowing the infection to get worse? These should precede decisions on the selection of agents, the correct dosages and the duration of treatment. Many of the usual answers to these questions are under review.

- Upper respiratory tract infection
- Urinary tract infection
- Food-borne pathogens: is food safe?
- Antibiotic resistance in community pathogens
- Impact of political, social, economic factors on community infection in Europe
- New vaccines
- New aspects in the antiviral therapy of herpes zoster infections
- AIDS/HIV and sexually transmitted infections

### THEME 2: Infections in surgical patients

Antibiotics and surgeons now march hand in hand. Much of modern surgery would not be possible without the support of

antimicrobial therapy yet surgeons' use of antibiotics is often criticized. Accusation of over-use, failure to prevent infections by non-compliance to hygienic measures and breeding of resistant bacteria in hospitals are still made (often without justification). Guidelines are now on the record to keep procedures up to scratch. In the intensive care unit there is debate over which multiresistant bacteria can be ignored and when they require action. Is the better use of antibiotics all that is required, anyway? Probably not.

- Common surgical infections
- Nosocomial surgical-site infections

- The surgical intensive care unit
- Tracing hospital infections
- Febrile neutropenia in cancer patients
- Advances in the management of neutropenia
- Cytomegaloviruses in the immunocompromised

### THEME 3: Regional problems

The region is defined as those areas contiguous to the southern and eastern Mediterranean Sea. This area is rich in infectious diseases because it includes a large part of eastern Europe (which has undergone severe social and political upheaval in recent years), the eastern seaboard with the desert sand

and heat behind and on the northern coast of Africa, and Greece and Turkey. There are many novel problems to discuss.

- Controlling antibiotic use and resistance in low resource setting
- Management of echinococcal disease
- Hepatitis in the eastern Mediterranean

### RESEARCH SYMPOSIA

#### Microbiology

- The implications of  $\beta$ -lactamases in Gram-negative infections
- Food-borne salmonellosis



## 23rd International Congress of Chemotherapy

7–10 June 2003  
Durban, South Africa



## 5th European Congress of Chemotherapy and Infection

17–20 October 2003  
Rhodes, Greece



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*continued on page 8*

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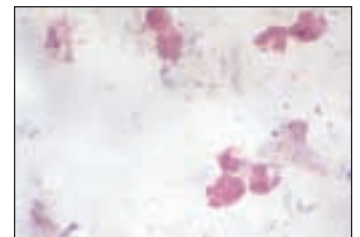
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## Epidemic meningitis in western Africa (Burkina-Faso)\*

An outbreak of meningitis caused by *Neisseria meningitidis* W135 occurred in 2002 in Burkina-Faso, western Africa. It was detected in February and continued until May, infecting more than 12 000 people and killing about 1 500. W135 had not been a primary cause of a major meningitis epidemic previously in Africa.

This outbreak has raised a few questions about treatment and prevention. An urgent search is under way for a more effective and affordable vaccine to meet future outbreaks. The only currently available vaccine is a 'tetravalent' vaccine containing strains A, C and W135. This vaccine is more expensive (US\$5) than a vaccine containing just strains A and C (25 cents). Also, because there has been little need for it, there is limited supply. Hence the vaccine is both unavailable and unaffordable in Africa. For effective epidemic control, about 2–5 million doses are needed.

Effective surveillance systems and the back up given by laboratories that could identify and confirm cases of meningitis caused by the organism must be in place. Currently, meningitis patients in Africa are being treated with chloramphenicol. A single dose of ceftriaxone has shown promise; however, it needs to be tested further if it is to be used widely as an alternative treatment. ■



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*Meningococci in cerebrospinal fluid.*

\*Source: WHO Press releases (WHO/69 and WHO/71, September 2002)

*continued from page 7*

- Reversal of resistance by modifying efflux pumps

### Virology

- Aseptic meningitis

### Mycology

- Lipid formulations of amphotericin B and other newer antifungals
- Invasive fungal infections in paediatrics
- Advances in the management of invasive fungal infections

### EXPERT LECTURES

1. History of surgical infection
2. SIRS versus sepsis
3. Is there a future for probiotics?
4. How should clinical trials of antibiotics be conducted?
5. Modification of clinical presentations of infectious disease by immunization in childhood
6. New look at pathogenesis and treatment of infective endocarditis
7. Resolved and unresolved issues in treatment of UTI

### POSTGRADUATE COURSE INCLUDING SYMPOSIA AND LECTURES

An example of a postgraduate session is shown.

#### A portrait of the pneumococcus today

- Virulence and pathogenesis
- Epidemiology of pneumococcal disease
- Antimicrobial resistance: mechanisms and epidemiology
- Treatment of invasive infections
- Pneumococcal vaccines

For further updates, contact: [jdw@ischemo.demon.co.uk](mailto:jdw@ischemo.demon.co.uk)

## Topics in Food Safety

### Honey – the streptomycin story

In February 2002, the sale of Chinese honey in the UK was banned when it was found to contain streptomycin. The discovery followed a European Union (EU) recommendation for the suspension of imports of Chinese Products of Animal Origin (POAO) because of concern over the lack of controls on the use of veterinary medicines and other products in China. The sequence of events and the context of the ban warrant close examination.

Following the EU recommendation, the UK Food Standards Agency (FSA) ordered tests on Chinese POAO in the shops and, surprisingly, honey was included in the testing programme. Fifteen samples were examined and seven were found to contain streptomycin. The FSA said the amounts found were small and the honey was safe to eat; however, the presence of streptomycin was illegal and the ban was imposed.

#### Test sensitivity

In general, whether or not a substance is deemed to be present in a substrate depends largely upon the sensitivity of the test used to detect it. Highly sensitive tests may detect very small amounts of substance and may even detect amounts naturally present in the

environment. For this reason, minimum residue levels (MRLs) may be set below those at which the amount of the substance is deemed safe and acceptable. If an MRL is simply set at the lowest level detectable, insignificant amounts of a substance may give positive results.

The test chosen by the FSA to detect streptomycin in the Chinese honey was extremely sensitive. Consequently, the amounts detected were extremely small – as low as 50 µg/kg in one case. Indeed, the amounts found were regarded as safe by the FSA, which stated that an adult would have to eat around eight jars a day for there even to be a potential risk.

This statement does not wholly demonstrate just how small were the amounts of streptomycin found. It is an antibiotic, which is still approved for the treatment of tuberculosis in man. The daily dose (which may be repeated for 2 months or more) is 1 g. It is not absorbed when given by mouth and must be injected. If it were absorbed, a consumer would have to eat 20 000 kg or 44 000 454-g jars of honey to ingest the 1 g daily dose.

The FSA stated, 'This is not a food safety issue ..... The products are being withdrawn

because honey cannot legally contain streptomycin', which begs the question, why was such a sensitive test employed? It resulted not only in the ban of Chinese honey, but in delays in honey distribution as the demand for sensitive tests for streptomycin and other antibiotics on honey from other countries grew.

#### Need for less sensitive tests?

It is now clear that the ban on Chinese honey was inconsistent. Within the EU, for example – in Austria, The Netherlands and Belgium – the agricultural use of streptomycin is permitted. It is also used in the USA. In Belgium it may be sprayed on apple and pear trees to prevent fire blight, a serious disease caused by *Erwinia amylovora*. The concentration in the spray solution is 108 mg/l, or 108 000 µg/l. The residue limit, below which level streptomycin is permitted to be present in the harvested fruit, is 125 µg/kg. Thus, the amount found in some of the Chinese honey samples would have been deemed acceptable in Belgian apples. The MRL for apples, like that for honey, was based on the maximum sensitivity of the test used to detect it; and therein lies a serious potential problem.

To prevent fire blight, apple and pear trees are sprayed with streptomycin once or twice during primary flowering. This is the time at which bees will be visiting the trees. Unless they take a shower before returning to their hives, the bees will inevitably carry streptomycin back with them and contaminate their honey. It will not be dangerous, but as more sensitive tests are developed, streptomycin will inevitably be detected in European honey. Moreover, as soil contains a huge number of bacteria, some of which produce streptomycin



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*Bees visiting trees sprayed with streptomycin will carry it back with them and contaminate their honey.*

naturally, it follows that infinitely sensitive tests will eventually detect small amounts of streptomycin on root vegetables.

This demonstrates that the concept of zero tolerance and the development of infinitely sensitive tests are incompatible. If the law is an ass, shouldn't we change it? Or in this case, would it not have been better and cheaper to use a less sensitive test for streptomycin – unless there was more to the story than meets the eye? ■



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## INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS

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# New concepts in antimicrobial treatment of acute exacerbations of chronic bronchitis

The aetiological role of bacterial pathogens and antimicrobial therapy for the management of acute exacerbations of chronic bronchitis (AECB) have long been areas of research and debate. Presentations at the recent 12th European Respiratory Society (ERS) Annual Congress in Stockholm, Sweden, September 2002, addressed some novel concepts in the antimicrobial treatment of this illness.

A substantial global socioeconomic burden is presented by AECB (Figure 1). Antimicrobial treatment in selected patient populations has been associated with lower relapse rates, longer periods between exacerbations, shorter duration of symptoms and reduced hospitalizations, all of which have cost implications.

The possible immunomodulatory effects of antimicrobial agents have received increasing attention and were reviewed recently.<sup>1</sup> Macrolides and fluoroquinolones have been shown to modulate cytokine expression in a variety of pre-clinical models. Data suggest that agents, such as moxifloxacin, that cause limited release of bacterial cell wall components may be associated with a consequent reduction in the host inflammatory response and this may contribute to faster relief from clinical symptoms.<sup>2</sup> The contribution that other direct effects on the host response may have to clinical success, e.g. upregulation of mucociliary beat frequency observed with moxifloxacin, are under investigation.

Clinical data from two new innovative moxifloxacin studies (IMPAC and MOSAIC) on chronic bronchitis and chronic obstructive pulmonary disease (COPD) were presented at the 12th ERS Annual Congress. Both studies enrolled patients during an exacerbation-free period and followed them long-term. They also allowed for the treating physician to exercise clinical judgement in the selection of comparator antimicrobial therapy. These studies have not

only captured valuable data about antimicrobial therapy, but also fundamental disease information for chronic bronchitis and COPD.

The IMPAC study is an observational, prospective study conducted over a 2-year period that followed the evolution of disease in patients with COPD.<sup>3</sup> Among other parameters, this study investigated the impact of different antibiotics (moxifloxacin versus choice of comparator – amoxicillin-clavulanate, cefuroxime, clarithromycin, azithromycin or other antimicrobial agents) on time to recovery from acute exacerbations of COPD. The investigators found that moxifloxacin produced significantly ( $P=0.026$ ) faster improvement of symptoms, with a mean of 4.7 days compared with 5.8 days for the other antibiotics (Figure 2).

The MOSAIC study is a multinational, double-blind, randomized study that compared the effectiveness of moxifloxacin (400 mg once daily for 5 days) with a standard 7-day regimen of amoxicillin (500 mg three times daily), clarithromycin (500 mg twice daily), or cefuroxime-axetil (250 mg twice daily) for the treatment of AECB.<sup>4</sup> Chronic bronchitis patients with a history of heavy smoking and recurrent

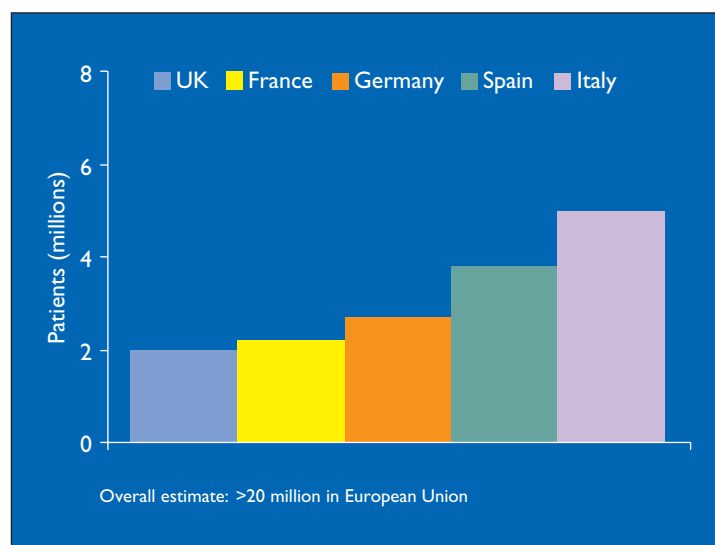


Figure 1: The impact of acute exacerbations of chronic bronchitis across Europe (data source: IMS Europe, 2001).

AECB episodes were enrolled. Their baseline status was established when they were well in terms of signs and symptoms, respiratory function and quality of life. Patients presenting subsequently with an infective exacerbation were randomized to antimicrobial therapy. In addition, patients were followed for up to 9 months post-antimicrobial treatment for AECB to assess long-term outcomes.

In the preliminary MOSAIC results (Figure 3), investigators found not only that moxifloxacin

was as safe as current standard regimens used in the management of AECB, but that patients treated with moxifloxacin had a significantly higher clinical cure rate (70%) than those given the comparator antibiotics (62%) (95% confidence interval [CI]: 0.3, 15.6). Similarly, moxifloxacin-treated patients experienced a significantly higher bacteriological response rate (92%) than those treated with the comparator drugs (81%) (95% CI: 0.4, 22.1).

The MOSAIC study is expected to continue to yield a wealth of

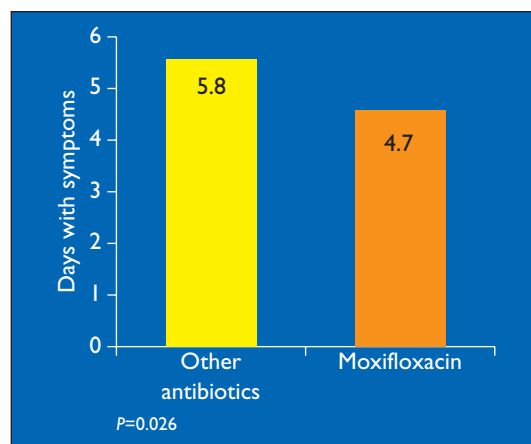


Figure 2: Mean duration of symptoms of acute exacerbations of chronic obstructive pulmonary disease, moxifloxacin versus standard antimicrobial treatment.<sup>3</sup>

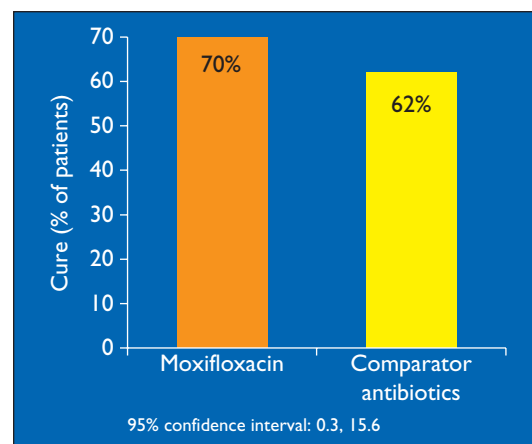


Figure 3: Clinical cure rate in patients treated with moxifloxacin versus standard therapy for acute exacerbations of chronic bronchitis.<sup>4</sup>

information about AECB and antimicrobial treatment, and sets a new standard for antimicrobial clinical studies in AECB.

### Conclusion

The demonstrated activity of moxifloxacin against novel pre-clinical and clinical end-points in AECB adds to the extensive experience with this agent. With over 13 million patient exposures,<sup>5</sup> moxifloxacin has established itself as a safe, clinically proven treatment for respiratory tract infections. Over 80 countries now have the oral formulation

and intravenous moxifloxacin is available in 20 countries. Patients around the globe can now benefit from an antimicrobial treatment for respiratory tract infections that is associated with rapid symptom resolution and superior clinical results. ■

**R Wilson, MD**  
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Publication of this article is part of the sponsorship of *Antibiotics Chemotherapy* provided by Bayer AG through an unrestricted educational grant.



## Disease Management Series – I



# Hot topics in urinary tract infections, Budapest, Hungary, 24–26 January 2003

This symposium is the first in the Disease Management Series (DMS) organized by the International Society of Chemotherapy (ISC). The DMS is a series of scientific meetings aimed at in-depth discussion on the optimal management of common infectious or malignant diseases.

The DMS is organized by the ISC in collaboration with the regional and national affiliated societies and with the corresponding regional and national societies also involved in the topic concerned. In Budapest, controversial issues in the management of urinary tract infection (UTI) will be discussed in great detail.

The ISC is very appreciative that, in addition to the Federation of European Societies for Chemotherapy and for Infection (FESCI) and the Hungarian Society for Chemotherapy, the European Society for Infection in Urology (ESIU) – affiliated to the European Association of Urology (EAU) – and the Hungarian Society for Urology are also part of the sponsoring scientific societies.

Participants are invited to present posters on their clinical and scientific work. The industries involved in the topic of the

conference will also be invited to present their views, e.g. by displaying a selection of posters, probably presented elsewhere, which best characterize their drugs. It is hoped that audience participation and a sharing of different views will lead to highly stimulating discussion.

An additional aim of the DMS is to bring together clinicians, scientists and industries to air their views and needs and listen to those of others in a co-operative and friendly atmosphere. Budapest is an ideal place for this. ■

**Jean-Claude Pechère**  
*International Society  
of Chemotherapy*

**Kurt G Naber**  
*European Society  
for Infection in Urology*

**Endre Ludwig**  
*Hungarian Society of Chemotherapy*

**Peter Tenke**  
*Hungarian Society of Urology*

## Programme

### I. Pathogenesis, Vaccination

Moderators: Endre Ludwig (Hungary), Silvester Krcmery (Slovakia)

- Virulence factors in *E. coli* – Levente Emödy (Hungary)

- Is vaccination possible? – Thomas M Hooton (USA)
- Management of UTI in diabetics – Andy Hoepelman (The Netherlands)
- Clinical significance of asymptomatic bacteriuria – Raul Raz (Israel)

### II. Uncomplicated UTI/Cystitis

Moderators: Jean-Claude Pechère (Switzerland), Otto Cars (Sweden)

- Epidemiology – ECOSENS – Study (update) – Gunnar Kahlmeter (Sweden)
- Do fluoroquinolones contribute to resistance in the treatment of uncomplicated UTI? – Thomas M Hooton (USA)
- Pivmecillinam, a drug of choice for the treatment of uncomplicated cystitis – Wolfgang Graninger (Austria)
- Why fosfomycin trometamol as first-line therapy for uncomplicated UTI? – Gian Carlo Schito (Italy)
- Round-table discussion

### III. Complicated and nosocomial UTI

Moderators: Ian Bishop (UK), Elizabeth Nagy (Hungary)

- Febrile UTI in men – Peter Ulleryd (Sweden)
- Controversies on perioperative prophylaxis – Magnus Grabe (Sweden)

- Prudent use of antibiotic therapy in nosocomial UTI – Kurt G Naber (Germany)
- Prevalence study of nosocomial UTI in urology – Truls Bjerkklund Johansen (Norway)

### IV. Encrustation and infection of urinary devices

Moderators: Bernhard Lobel (France), Joan Palou Redorta (Spain)

- Biofilm infection in UTI – Peter Tenke (Hungary)
- Prevention of catheter-associated UTI – Mete Cek (Turkey)
- Phosphorylcholin-coated ureteral stents – Alex Heidenreich (Germany)
- Is silver coating effective? – Josef-Peter Guggenbichler (Germany)
- Round-table discussion

### For further information

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## 23rd ICC – Scientific Programme



**Durban, South Africa, 7–10 June 2003**

On a global level, malaria, AIDS and tuberculosis progress, new infections emerge, antibiotic resistance escalates, and

some forms of cancer multiply. The 23rd International Congress of Chemotherapy (ICC) programme is aimed at the review of different strategies for improving management of infectious diseases

and cancers, including breakthrough of high science, better understanding of pathogenesis and mode of transmission, evidence-based protocols, new targets and new drug discoveries. ■

For further information, please contact:  
23rd ICC Secretariat, Congrex  
Holland bv, AJ Ernststraat 595K,  
1082LD, Amsterdam, The Netherlands  
E-mail: [icc2003@congrex.nl](mailto:icc2003@congrex.nl) or  
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[www.congrex.nl/icc2003](http://www.congrex.nl/icc2003)

### PLENARY LECTURES

- Expanding access to healthcare
- Global movement of antibiotic resistance
- Research ethics in developing countries
- New drug targets for tuberculosis
- Viruses causing cancer: an opportunity for new diagnostic tools and therapeutic targets
- Bad and good in the epidemiology of malaria
- Strategies of drug design after completion of the genome project
- Anti-influenza drugs: new diagnostic and therapeutic challenges
- Quorum sensing as a bacterial virulence attribute
- Challenges in HIV infections: fears and hopes
- Where HIV and cancer meet

### PRE-CONGRESS SYMPOSIA

- I. Primary healthcare symposium
  - A. Primary healthcare protocols for the management of patients with common infections
    - A1. Tuberculosis
      1. Diagnosis
      2. Treatment
      3. Dealing with treatment failures
    - A2. Diarrhoea
      1. Clinical symptoms and aetiology: differentiating the syndromes
      2. Management of watery diarrhoea
      3. Management of bloody diarrhoea
    - A3. Acute respiratory tract infections
      1. Aetiology of respiratory tract infections
      2. Management of the child with middle ear infection
      3. Management of patients with pneumonia
    - A4. Sexually transmitted infections
      1. Syndrome recognition
      2. Syndromic management
      3. Management of patients with failures
  - B. Infection control protocols

### II. Urinary tract infections

- Do we need guidelines for UTI?
- UTI in African infants
- Outcome from the NIH prostatitis study
- Nanobacteria: myth or reality?

### III. Evidence-based dosage regimens for antibacterial agents

### IV. Reproductive health and infection

### INFECTIOUS DISEASE TRACK

#### ID I. Malaria update

1. Treating severe malaria
2. Progress on malaria vaccines
3. Reversal resistance in *P. falciparum* infections: an innovative approach
4. Malaria in travellers – chemoprophylaxis and self-treatment
5. Have artemisinin-based combinations lived up to their expectations?
6. HIV and malaria
7. Control of malaria

#### ID II. Challenges in the treatment of tuberculosis

1. Treating latent TB infection
2. Multidrug resistant TB – therapy update

#### ID III. Laboratory issues in tuberculosis

1. Tuberculosis diagnostics: a new generation?
2. Relapse, re-infection and cure

#### ID IV. Limiting mortality in community-acquired pneumonia

1. Why do patients still die from pneumococcal disease?
2. Failures on  $\beta$ -lactam therapy
3. Failures on fluoroquinolone therapy
4. Failures on macrolide therapy
5. Vaccines

#### ID V. New views on treatment of pneumonia

1. Empiric treatment: monotherapy versus combined therapy
2. The role of fluoroquinolones in CAP
3. The role of ketolides in CAP
4. Are all carbapenems alike?

#### ID VI. Infections in intensive care units

1. Management of severe intra-abdominal infections in ICU
2. Targeted interventions to prevent infections in the intensive care unit
3. Are invasive techniques necessary in the diagnosis of VAP?
4. PK/PD correlation parameters are mandatory for outcome

#### ID VII. Infections by Gram-positive cocci

1. MRSA, VISA, VRE and other resistant Gram-positives: combatants in the same fight?
2. Community-acquired MRSA
3. Current and future treatment options for Gram-positive infections

#### ID VIII. Hot issues in management of meningitis

1. Why and when to use steroids in the management of meningitis
2. New developments in vaccines for meningococcal meningitis
3. Diagnosis and management of fungal meningitis

#### ID IX. New antibacterials

1. Emerging drugs
2. Is the source of new antibacterial drugs drying out?

#### ID X. Macrolides and biofilms

#### ID XI. Infection control

1. Evidence-based protocols in healthcare and hospital
2. Are antibiotics a substitute for good IC practices?
3. The cost-effectiveness of infection control programmes

#### ID XII. Learning from each other: impact of culture and tradition on nosocomial infections (round-table discussion)

#### ID XIII. Sexually transmitted infections and HIV transmission

1. HIV and STIs – what have we learnt?
2. HSV and HIV transmission
3. The role of vaginal microbicides in preventing HIV and other sexually transmitted infections

#### 4. Does HIV co-infection alter the response to treatment of STIs?

#### ID XIV. That identification of the aetiological agent is important in management of STDs: a debate

1. Is syndromic management the answer for sexually transmitted infections?
2. Controlling STDs with appropriate diagnosis

#### ID XV. Towards better control of tropical diseases

1. Towards the eradication of trachoma
2. Eradication programmes for filariasis
3. New drugs for parasitic infections
4. Leptospirosis: a re-emerging infection

#### ID XVI. Immunomodulation

1. Immunomodulatory actions of antibiotics: friend or foe?
2. The pros and cons in the new approaches for controlling sepsis

#### ID XVII. Immunization

1. Childhood immunization
2. Adult immunization
3. Newer approaches to vaccines
4. New vaccines for common diseases

#### ID XVIII. Progress in antifungal therapy

1. New drugs and new formulations
2. PK/PD aspects of antifungal drugs
3. Pharmacokinetics and tissue penetration of amphotericin B formulations

#### ID XIX. Are haemorrhagic fevers progressing?

1. Haemorrhagic fevers as a biologic weapon
2. Molecular epidemiology of Ebola fever
3. Emerging haemorrhagic fevers

#### ID XX. Management of viral infections

1. Prevention and treatment of CMV in transplantation
2. EBV-induced lymphoproliferative disorders
3. Vaccine development for the control of viral gastroenteritis

**ID XXI. Latest developments in the management of hepatitis**

1. New insights in the diagnosis of hepatitis B
2. Chemotherapy for hepatitis B
3. Chemotherapy for hepatitis C

**HIV/AIDS TRACK**

**HIV I. Epidemiology and primary prevention**

1. Update on primate lentiviruses
2. Global HIV trends
3. Voluntary counselling and testing centres
4. Modifying behaviour in Africa

**HIV II. Antiretroviral therapy**

1. Antiretroviral therapy – state of the art
2. Treating children with ART
3. Structured treatment interruptions
4. Adherence
5. Cost issues

**HIV III. Opportunistic infections**

1. Impact of HIV infection on

1. pneumonia in children
2. HIV and tuberculosis

**HIV IV. Preventing mother to child transmission**

1. Overview of antiretroviral therapy to prevent MTCT
2. European experience
3. Relevance of nevirapine resistance after single-dose MTCT use
4. Breast-feeding in resource-poor settings

**HIV V. Laboratory issues**

1. Therapeutic drug monitoring
2. Resistance testing
3. Towards affordable monitoring

**HIV VI. Vaccine development**

1. HIV vaccine progress
2. Ethical issues in developing a vaccine site
3. Prime-boost strategy

**ANTICANCER CHEMOTHERAPY TRACK**

**CA I. Targeted therapy: a revolutionary approach**

1. Developing the concept

2. Tyrosine kinase inhibitors
3. Monoclonal antibodies and vaccines
4. Other targeted therapies

**CA II. Controlling the pain**

1. Magnitude of the problem
2. Bisphosphonates
3. Non-steroidal anti-inflammatory drugs

**CA III. Management of infections in oncology**

1. Evolving antifungal therapy in cancer patients
2. Febrile neutropenia

**CA IV. Haematology**

1. Perspectives in chronic granulocytic leukaemia
2. Changing approach to myeloma
3. The myelodysplastic syndromes

**CA V. Anticancer chemotherapy**

1. Pharmacological strategies to overcome tumour drug resistance: rationale and clinical achievements
2. Pharmacogenomic and

3. pharmacogenetic determinants of drug response: towards tailored drug therapy in oncology
3. Renal dysfunction following chemotherapy and bone marrow transplantation

**'MEET THE EXPERT' SESSIONS: MANAGEMENT OF COMMON DISEASES**

These are interactive discussions between experts and meeting participants. Topics include:

- Otitis media
- Pharyngitis
- Urinary tract infections
- Diarrhoea
- Sexually transmitted infections
- Necrotizing fasciitis
- Impetigo/cellulitis
- Hepatitis
- Pneumonia
- Pelvic inflammatory disease
- Malaria
- Tuberculosis

**5th IACMAC Conference – 'Antimicrobial Therapy'**

The Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC) in Russia was founded in 1997 to improve quality of diagnostics, prophylaxis and treatment of infectious diseases and to develop research in the field of antimicrobial chemotherapy and clinical microbiology in the Russian Federation.

Annual international conferences have been organized by IACMAC since 1997. In 2002, the conference (held in Moscow, Russia, 4–6 June), traditionally organized under the auspices of the Ministry of Health of Russia and the Institute of Antimicrobial Chemotherapy, Smolensk, was also supported by the International Society of Chemotherapy, the American Society of Microbiology, the European Society for Clinical Microbiology and Infectious Diseases, the British Society for Antimicrobial Chemotherapy, the Italian Society of Chemotherapy, the Spanish Society of Chemotherapy and the Alliance for Prudent Use of Antibiotics Society. More than 1500 participants from 76 regions and 130 cities of the Russian Federation and countries of the former Soviet Union attended the scientific meeting. Over 332 abstracts were submitted and 26.5% (88) of them were selected for publication.

**Conference highlights**

The conference was preceded by a workshop on 'Modern models of monitoring of antimicrobial resistance and possibilities of their use in Russia'. The European, American and pharmaceutical industry views were presented by JD Williams (UK), J Hindler (USA), J Poupard (USA) and G Kahlmeter (Sweden). S Sidorenko covered specific problems of susceptibility testing in Russia. The keynote lecture on 'The Human and the Bacterium: could Goliath win?' by J-C Pechère (Switzerland) provided an exceptional onset for the conference. The Russian folklore ensemble of Dmitry Pokrovsky performed at the conclusion of the opening ceremony.

The conference topics included issues of bioterrorism, new therapeutic options for community-acquired and nosocomial infections caused by various bacterial pathogens, new possibilities in the therapy of viral infections, strategies for selection of antibacterial agents in hospital and intensive care units, and general perspectives of anti-infective therapy in the new millennium. Special symposia were devoted to therapy of sepsis, urinary tract infections, community-acquired pneumonia and current approaches in overcoming resistance of *Pseudomonas aeruginosa*.

All lectures and slide presentations were translated into



*Panel of speakers at the 5th IACMAC.*

Russian and English. The international specialists and the participants from Irkutsk, Penza, Ufa, Murmansk, Krasnodar, Kiev and Tashkent addressed many important questions.

**Colloquium: 'Antibiotics without Ties'**

A colloquium, 'Antibiotics without Ties', was held during the post-conference boat tour to Saint Petersburg and the beautiful islands of North Russia – Valaam and Kizhi – situated on the Ladoga and Onega Lakes. Ten lectures were presented by four international and six Russian speakers. The topics discussed included: peculiarities of pharmacokinetics and pharmacodynamics of antibiotics (M Jacobs, USA); the necessity of new agents for the treatment of fungal infections (N Klimko, Russia); staphylococcal and enterococcal infections (J-C Pechère, Switzerland); and the place of the 'immortal' drug amoxicillin/clavulanate (P Appelbaum, USA). Issues of the role of

intravenous fluoroquinolones in the treatment of severe infections (E Rubinstein, Israel) and perspectives of step-down therapy of infections in hospitalized patients (L Stratchounski, Russia) were also presented. In general, all participants considered the tradition of holding post-conference tours successful, and this will have been duly noted by the organizers of future meetings. ■

'Surgical Infections: Prevention and Management' will be the theme for the 6th IACMAC meeting (29–30 May 2003) – as part of a Disease Management Series Meeting, an ISC initiative. Information about this meeting is available at: [www.antibiotic.ru](http://www.antibiotic.ru), or by e-mailing [galkin@antibiotic.ru](mailto:galkin@antibiotic.ru) or [moosdeen@ischemo.demon.co.uk](mailto:moosdeen@ischemo.demon.co.uk)

We welcome all those who are interested in attending.

**Dmitry Galkin**  
General Secretary of IACMAC

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pipemidic acid (1972), discovered by the Dainippon Pharmaceutical Co. Ofloxacin, another fluoroquinolone agent used worldwide, was synthesized by Daiichi Pharmaceutical Co. in 1980 and licensed to Hoechst in Europe and Johnson & Johnson in the USA.

In 1975, a collaborative anticancer project between the Umezawa group and the Mercian Co. led to the discovery of aclarubicin, a microbial product. The less cardiotoxic agent pirarubicin (synthesized by the Umezawa group, 1979) was discovered when a semi-synthetic approach was applied to the anthracycline class of anticancer antibiotics.

Continuing research on bleomycin was undertaken to obtain more active and safer derivatives, and peplomycin (previously pepleomycin) was synthesized in 1974 by Nippon Kayaku Co.

The microbial product mizoribine (previously brendenin), a unique compound showing protective effects against influenza-virus infection in mice, was identified in 1973 by Toyo Jozo Co. Its protective mechanism was due to a reduction of hypersensitivity in mice. Mizoribine was successfully developed as an immunosuppressant for tissue/organ transplantation, 3 years before cyclosporin.

Avermectin, an antihelmintic agent discovered in 1977 following collaborative research between the group of Professor Satoshi Omura (Kitasato Institute) and Merck Research Laboratories, is used to control infections in livestock and domestic animals. However, this agent is also beneficial for humans in equatorial regions for the prevention and treatment of onchocerciasis.

Between 1966 and 1980, there were other advances in agricultural and veterinary research. Validamycin (for plant protection) and bialaphos (weed control) were discovered by Takeda Chemical in 1971 and by Meiji Seika Kaisha in 1973,

respectively. Interestingly, voglibose, an inhibitor of  $\alpha$ -amylase used for blood sugar regulation, was discovered during research of validamycin. Other compounds discovered during this period and used in animals are: sedecamycin (1966, Takeda Chemical); bicozamycin and thiopeptin (in 1969 and 1970, respectively, Fujisawa Pharmaceutical); acetylisovaleryltylosin (1971, Mercian); salinomycin (1974, Kaken Chemical Co.); milbemycin (1974, Sankyo Co.); mirosamicin (1980, Toyo Jozo Co.); nanafrocin (1975, Kitasato Institute); and benofloxacin (1980, Otsuka Pharmaceutical Co.).

#### **Modern technology (1981–1990)**

In 1967, the Umezawa group, pioneers of anticancer research using antibiotics, looked into the modulation of enzymes and immunological functions that are involved in various human pathological processes. The group's first enzyme inhibitor was cofomycin (a biochemical reagent) followed by over 50 novel enzyme inhibitors and more than 10 immunomodulators. Of these, ubenimex (1975, named bestatin) has been used clinically as an immunopotentiator in cancer, and guserimus (1985, previously called 15-deoxy-spergualin) as an immunosuppressor in organ transplantation. Another 10 or so compounds including leupeptin, pepstatin and antipain have been used worldwide as specific biochemical reagents.

Exploratory studies of enzyme inhibitors and immunomodulators led to the discovery of two beneficial drugs for human quality of life: pravastatin (1983, Sankyo Co.) for hyperlipidaemia and tacrolimus (1986, Fujisawa Pharmaceutical) for immunosuppression in transplant patients. Clinical application of tacrolimus was later extended to treatment of atopic diseases. Voglibose (a derivative of the sugar moiety of validamycin, discovered by Takeda Chemical in 1993) has



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*Over 117 useful antibiotics and related agents have originated from Japan.*

been used to control blood sugar levels in diabetics.

Following the successful syntheses of norfloxacin and ofloxacin, new fluoroquinolones with more potent activity and more favourable pharmacological properties, including lower toxicity, have been developed and used worldwide. These include: lomefloxacin (1984, Hokuriku Seiyaku Co.); tosfloxacin (1985, Toyama Chemicals); sparfloxacin (1987, Dainippon Pharmaceutical); levofloxacin (1987, Daiichi Pharmaceutical Co.); grepafloxacin (1988, Otsuka Pharmaceutical Co.); and gatifloxacin (1990, Kyorin Pharmaceutical). Other fluoroquinolones such as the oral preparations enoxacin (1978, Dainippon Pharmaceutical) and fleroxacin (1984, Kyorin Pharmaceutical) and the topical agent nadifloxacin (1980, Otsuka Pharmaceutical Co.) are licensed in Japan. Orbifloxacin, a unique analogue of sparfloxacin (1987, synthesized by Dainippon Pharmaceutical) was developed for chemotherapeutic use of livestock and domestic animals.

Clarithromycin (1984, Taisho Pharmaceutical Co.) marked another distinctive period in Japanese antibiotics. It is a derivative of erythromycin (methylation of a hydroxyl group of the 14-membered macrolide nucleus) that leads to extreme stability of the

derivative against stomach acidity. High absorption and serum levels of clarithromycin are achievable, and as a result, urinary excretion at concentrations effective against *Chlamydia* infection were noted. Abbott have marketed clarithromycin worldwide.

Japanese industries have undertaken extensive research in the  $\beta$ -lactam antibiotics, following the discoveries of cefazolin, piperacillin and cefotetan. Several novel  $\beta$ -lactam antibiotics have been used worldwide, including: the cepheps cefixime (1982, Fujisawa Pharmaceutical), cefprozil and cefepime (1983, Bristol-Banyu), cefpodoxime pivoxil (1984, Sankyo Co.), ceftibuten (1985, Shionogi), cefditoren pivoxil (1985, Meiji Seika Kaisha); the carbacephem meropenem (1987, Sumitomo Chemical); of the carbapenems, loracarbef (1987, Kyowa Hakko); and a  $\beta$ -lactamase inhibitor, tazobactam (1984, Taiho Pharmaceutical Co.). In response to clinical demands, additional  $\beta$ -lactam antibiotics were developed for domestic use: the penicillin lenampicillin (an ester of ampicillin, 1981, Kanebo Pharmaceutical Co.); the cepheps cefminox (1981, Meiji Seika Kaisha), cefzonam (1984, Lederle Japan Co.), cefteteram pivoxil (1987, Toyama Chemical), cefotiam hexetil (1985, Takeda Chemical), cefdinir (1987, Fujisawa

Pharmaceutical), cefcapene pivoxil (1989, Shionogi) and cefozopran (1989, Takeda Chemical); the oxacephem, flomoxef (1982, Shionogi); the carbapenems, panipenem (1985, Sankyo Co.) and faropenem (1986, Suntory Co.); and the monobactam carumonam (1983, Takeda Chemical).

#### Research, development and future trends (from 1991)

Current research and development in the  $\beta$ -lactam field has been directed mainly at the carbapenem class. A parenteral carbapenem, S-4661 (reported by Shionogi in 1994), is in Phase III trials in Japan; E1010 (reported by Eisai Co. in 1995) is in Phase I study in the USA. L-084, an orally active carbapenem discovered by Lederle Japan in 1998, possesses favourable activity against resistant pneumococci and is being considered for international development. Another orally active carbapenem, CS-834 (reported by Sankyo Co. in 1996), is in clinical trials in Japan.

Among the cepheids, cefoselis, a parenteral agent synthesized by Fujisawa Pharmaceutical in 1991, is being used in Japanese clinics. As orally active agents, ceftizoxime alapivoxil (developed by Asahikasei Co., produced by Kyoto Pharmaceutical Industries since 1990) is under review for New Drug Application (NDA) by the Ministry of Health, Labour and Welfare (MHLW), and S-1090, produced by Shionogi in 1992, is in Phase III clinical trials.

Research with fluoroquinolones has resulted in US and European evaluation of a very potent compound, sitafloxacin (synthesized by Daiichi Pharmaceutical Co. in 1991), for infections caused by resistant bacteria including MRSA and VRE. T-3811E, a unique quinolone derivative lacking fluorine at the 6-position (1997, Toyama Chemical), is in Phase III trials conducted by Bristol-Myers Squibb in the USA. In Japan, a parenteral, pazufloxacin tosylate (1990,

Toyama Chemical), and an orally active fluoroquinolone, prulifloxacin (1989, Nippon Shinyaku Co.), are undergoing review for NDA by the MHLW.

Several azoles of Japanese origin are being evaluated as antifungal agents in the USA and Europe. These include: ravuconazole, synthesized by Eisai in 1995 (code number ER-30346, being developed by Bristol-Myers Squibb); a series of azoles synthesized by Takeda Chemical, TAK-187 (1996) and TAK-456/TAK-457 (2000); and azoles first reported in 2000 by SSP Co., SS750, and by Sankyo Co., CS-758 (originally named R-120758). These novel antifungals possess favourable activity against yeast-form *Candida* and filamentous fungi, including *Aspergillus*.

Another class of antifungal, micafungin of the echinocandin class, was discovered by Fujisawa Pharmaceutical in 1998. Micafungin has been evaluated clinically in the USA and Europe and is under review for NDA by the MHLW. It shows excellent activity against *Candida* infections including cases caused by azole-resistant strains, and is effective in *Aspergillus* infections.

Antiviral research has not been strong in Japan, particularly in anti-HIV chemotherapy. Emivirine (MKC-442) was the first anti-HIV agent to be discovered in Japan, in 1997, by Mitsubishi Chemical Co. and developed by Triangle Pharmaceuticals. This reverse transcriptase inhibitor is being introduced in the USA. The second is a novel anti-HIV agent, TAK-779, that is an antagonist of the HIV-receptor CCR5 of CD4-cells. This was discovered by Takeda Chemical in 1999.

T-705 is an anti-influenza agent (2000, Toyama Chemical) with a simple structure and potent activity. This agent has received many licensing proposals from European and US pharmaceutical companies.

Today, the major thrust in anti-infective drugs in Japan focuses on antifungals and antivirals rather than antibacterials. Although some protozoal infections, caused by agents

such as *Cryptosporidium*, have become problematic in Japan, little attention has been given to the discovery of antiprotozoal agents.

Several novel anticancer and immunomodulatory agents of Japanese origin are being evaluated in Europe and the USA. NM-3 (a derivative of an angiogenesis inhibitor, cytogenin, discovered by the Institute of Microbial Chemistry) is in Phase I study in Europe and will soon undergo therapeutic study in the USA.

Japan leads the world in research on microbial products as anti-infective drugs. Among 136 novel anti-infective compounds of microbial origin published in the *Journal of Antibiotics* during 1991–2000, 71 were discovered in Japan. Several of these natural compounds are likely to be important lead molecules for the production of useful anti-infective agents. From 1991 to 2000, of the 88 institutions worldwide that have described novel anti-infective agents, there were 30 (34%) Japanese pharmaceutical companies, 27 European and US biopharmaceutical companies (31%), 14 European (16%) and 13 US (15%) pharmaceutical companies (Program and Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy).

The Japanese Society of Chemotherapy (JSC) has played an important role in promoting anti-infective and anticancer agents. The JSC has produced guidelines on antimicrobial susceptibility testing, determination and application of MIC-breakpoints and clinical evaluations in respiratory or urinary tract and surgical infections. JSC committee activities relating to publications, clinical evaluations, international affairs and other matters have expanded the development of new therapeutic agents. The impressive record of 110 JSC symposia devoted to new drugs has covered every major anti-infective agent in use, and many agents expected to be used in future. In addition, the

JSC has developed good working relationships with domestic and overseas pharmaceutical industries, authorities and organizations.

#### Acknowledgement

The authors thank Professor Julian E Davies, The University of British Columbia, Vancouver, Canada, for his help and encouragement. ■

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of Chemotherapy

Morimasa Yagisawa  
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## Diary Dates

### ISC Meetings

#### 24–26 January 2003, Budapest, Hungary

Hot Topics in Urinary Tract Infections (ISC Disease Management Series)

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Fax: +36 1 456 0888  
E-mail:  
convention.budapest@mail.datanet.hu

#### 29–30 May 2003, Moscow, Russia

Surgical Infections: Prevention and Management (ISC Disease Management Series)  
**CONTACT:** Professor Leonid Stratchounski, Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC), PO Box 60,

Smolensk 214019, Russia.  
Tel: +70 812 611 301  
Fax: +70 812 611 289  
E-mail: str@antibiotic.ru

#### 7–10 June 2003, Durban, South Africa

23rd International Congress of Chemotherapy  
**CONTACT:** 23rd ICC Secretariat, Congrex Holland bv, AJ Ernststraat 595K, 1082 LD, Amsterdam, The Netherlands.  
Tel: +31 20 50 40 200  
Fax: +31 20 50 40 225  
E-mail: icc2003@congrex.nl

#### 10–12 September 2003, Huntsville, Ontario, Canada

First Conference on Community Acquired Pneumonia (ISC Disease Management Series)  
**CONTACT:** Felicissimo & Associates, Inc., CAP 2003 Conference, 205 Viger Avenue West, Suite 201, Montreal QC, Canada H2Z 1G2.  
Tel: +1 514 874 1998  
Fax: +1 514 874 1580  
E-mail: info@fa-events.com

#### 17–20 October 2003, Rhodes, Greece

5th European Congress of Chemotherapy and Infection (ECC-5)  
**CONTACT:** Congrex Sweden AB, PO Box 5619, Linnegatan, 89A, SE-114 86 Stockholm, Sweden.  
Tel: +46 8 459 6600  
Fax: +46 8 661 9125  
E-mail: congrex@congrex.se

### Other Meetings

#### 16–19 October 2003, Portofino, Italy

3rd International Meeting on Antimicrobial Chemotherapy in Clinical Practice (ACCP)  
**CONTACT:** Progetti di Congress Studio srl, Piazzale S. Turr 5, 20149 Milan, Italy.  
Tel: +39 02 319 6951  
Fax: +39 02 3360 4939  
E-mail: info@congress-studio.it

#### 14–16 November 2003, Berlin, Germany

2nd International Symposium on Resistant Gram-positive Infections  
**CONTACT:** K.I.T. GmbH,

Convention and Incentive Organization, Kurfürstendamm 71, D-10709 Berlin, Germany.  
Tel: +49 30 2460 3240  
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E-mail: rgpi@kit.de

#### 7–10 December 2003, Kuala Lumpur, Malaysia

6th Asia Pacific Congress of Medical Virology  
**CONTACT:** Dr Yasmin Malik, Department of Medical Microbiology, Hospital Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia.  
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these new agents with standard combination chemotherapy. This has been done in large Phase III trials in NSCLC but data are not yet available from these studies.

#### Other agents

Chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumours, with high levels of the appropriate target ligand, respond very well to a new marketed oral agent imatinib mesylate (Gleevec™/Glivec™ or ST1571 – Novartis). This agent was specifically designed to inhibit the tyrosine kinase coded for *bcr-abl* gene rearrangement seen in CML. A preliminary trial with this drug in small-cell lung cancer patients (SCLC) was negative but it did not include many patients with the target (*c-kit*) ligand. Further studies are under way to see if subsets of SCLC patients (with *c-kit*) will actually benefit. It has also been combined with interferon and cytarabine in CML patients, but the randomized study results are not yet published,

although preliminary data are very encouraging with a much-improved progression-free survival, reduced toxicity and higher achievement of a PH-chromosome negative status. The first monoclonal antibody approved for the treatment of cancer was rituximab, a chimeric antibody directed against the B-cell antigen, CD20, which is used for indolent lymphomas. It is therefore clear that some of these new agents need to be used only in patients with the appropriate target, while others may work without it.

#### The next few years

A major issue with all these agents will be cost. They often need to be taken for long periods of time, perhaps even for an entire lifetime. The cost may only be possible to deal with in very developed countries and not the developing world, as we have already seen with AIDS. The issue of resistance to these types of drugs is only just being considered but could become a major problem as it has with AIDS drugs, antimicrobial agents and standard cancer

chemotherapy. This will only become clear, along with data on potential late toxicities, in the next few years, as patients on these new drugs are followed closely by their oncologists. How these agents can best be combined with other more established cancer therapies will also be the subject of many clinical trials over the next few years.

This approach to cancer is relatively new, although it is really the basis of all chemotherapy (for infection, AIDS and cancer) and comes as no real surprise to those of us who believe in a unified 'chemotherapy' concept. Future discoveries in this type of therapy promise to be an exciting development in the field of cancer therapy. We will all be following this subject very closely over the next few years.

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