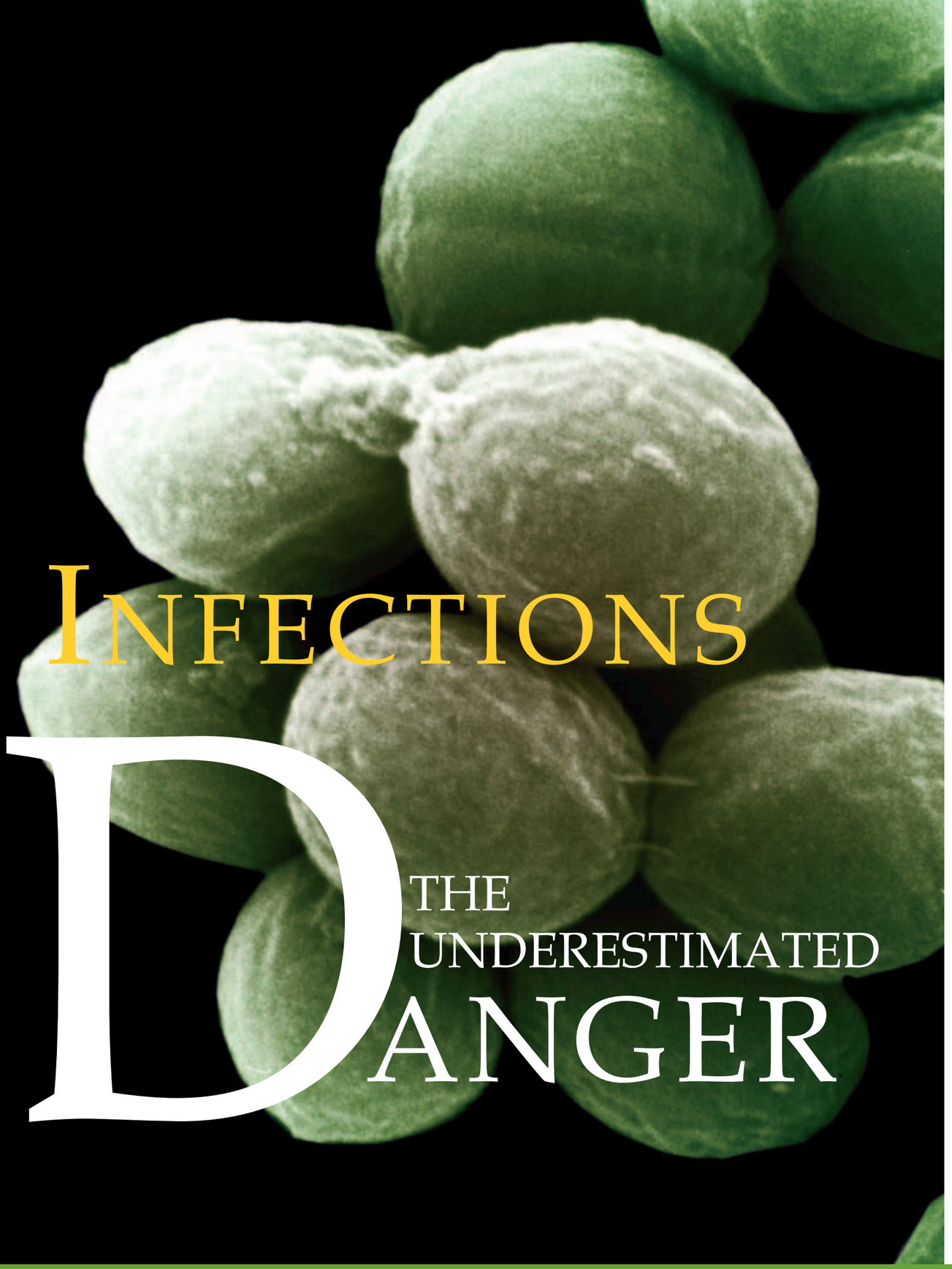


INFECTIONS

THE UNDERESTIMATED DANGER

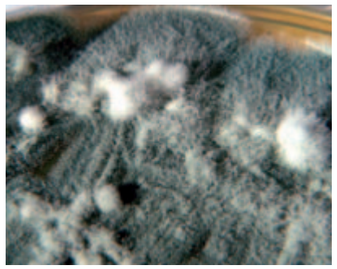
One morning in 1928 Alexander Fleming stood in his lab and was pretty unsatisfied with one of his experiments. Several days ago he transferred a bacterial culture on an agar plate with nutrient solution for continuous growth. What he realized that morning, was a green, fluffy-looking fungal culture which had sneaked into the plate as an "impurity" and now spread over the whole plate. Surprisingly, no bacteria grew at the outer edges of this fungal culture. Fleming drew the right conclusion from this observation: He later found out that the fungus, a member of the family of Penicillium, produces a substance which inhibits the growth of bacteria and he called this unique substance penicillin. Thanks to penicillin the number of fatal infections from injuries was drastically decreased.

"Golden Age"

Manifold ***antibiotics*** have been discovered and developed as a pharmaceutical drug until the end of the 60's of the last century. Thereby, the spectrum of different pathogens which could be successfully combated was significantly extended further. People believed that bacterial infection had been finally defeated forever. During this era US Surgeon General, William H. Stewart announced for instance, … "that we essentially defeated infectious diseases and could close the book of them…". This time is called the "golden age of antibiotics", and today most people still think that the available antibiotics have the power to successfully hold the life-threatening germs at bay – but today's reality is different. Meanwhile even the "reserve antibiotic" ***vancomycin*** has lost its function as the last reliable resource.

Already three decades ago it was discovered that an antibiotic looses its primary function after a longer period of medical application. In many clinics and elderlie's homes of the western society, also in Germany, the proportion of resistant human threatening pathogens is more than 20% by now. Thus, every day we face serious problems in the therapy with antibiotics. In the US about two million patients are infected with locally distributed pathogens in clinics every year; 3-5% of those infections show mortal progression (Infectious Disease Society of America, 2004). Another survey shows that more than 50 million people worldwide are infected with ***multi-resistant*** tuberculosis strains which cannot be treated with the known regular antibiotics (***World Health Organization***, 2004). The pathogens fight back; many antibacterial agents actually cannot harm them. Today, an increasing number of patients of all ages who suffer from an initially small infection or a normally routine surgery have to die.

Nobel prize laureate Alexander Fleming



Penicillium culture on agar plate

The worse is yet to come? How could that come about? What went wrong? Only twelve times vulnerable?

From the approximately 12.000 antibiotics which have been isolated from bacteria and fungi so far only about 100 compounds are in clinical use. The predominant proportion of the approved antibiotics worldwide are natural products or derive from natural product structures. It is evident that nature provides compounds which inhibit the growth of pathogens or even kill them.

Antibiotics
Compounds - frequently from microbial origin - which are able to kill bacteria (bactericide) or to inhibit their progeny (bacteriostatic).

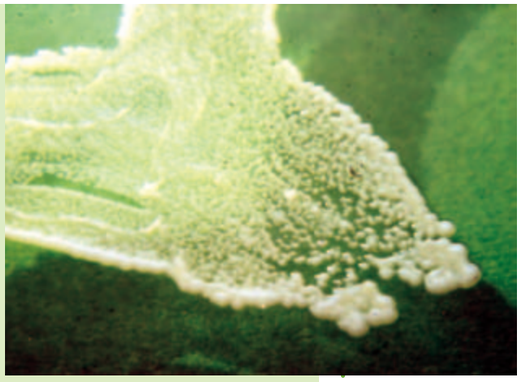
Fleming, Alexander
Scottish bacteriologist, born in Lochfield Darvel, August 6th, 1881. He was awarded the Nobel Prize 1945 for his discoveries being among the most important ones in the 20th century. Sir Alexander Fleming died in London on March 11th, 1955.

Multiresistent
By definition, more than four routine antibiotics are not active against a multiresistant pathogen which had been significantly affected before emergence of resistance in this strain.

Vancomycin
A glycopeptide antibiotic which is produced by actinomycetes strains of the genus ***Amycolatopsis***. Vancomycin inhibits cell wall formation of the growing pathogens. Since 1980 it has been applied against infections with multiresistant staphylococcus strains, and till 1987 it was a "reserve" antibiotic without any resistance problems.

World Health Organization (WHO)
Founded on April 17th, 1948, the organization has 192 member states with head office in Geneva/Switzerland, and is subordinated to the United Nations (UN). Aim of the WHO is to reach an optimum of health status for all people concerning physical, mental and social wealth.

Fleming and Hayden, 1909



Staphylococcus aureus on agar plate

Todays clinically applied antibiotics only have twelve different targets in the bacterial cells, though. For example, penicillins inhibit the formation of the bacterial cell wall, the ***tetracyclines*** disrupt protein production, and ***quinolones*** like ciprofloxacin affect the genetic material. Modern science estimates that the bacterial cell environment obtains more than 100 putative targets to stop bacterial growth. However, those targets have to be discovered by intensive investigation efforts first, and then the respective antibiotics need to be found.

Todays known and targeted twelve "weak spots" of bacteria are able to alter by mutations. Thus, the regularly used antibiotics do not bind to those special targets any more. Alternatively, bacteria can deactivate antibiotics by enzymatic reactions, e.g. β-lactamases inactivate penicillins. Or bacteria develop specific "pumps" which efficiently remove inflowing antibiotics from the cell thereby inhibiting the medicative effect. The malicious thing about resistance is that different types of resistances are manifest in the genes of bacteria. And that all genes - once acquired by a bacterium – can be transferred to other bacteria. This is mediated by normal, frequent gene exchange among bacteria. Hitherto, continuous research has a lead over the adaptability of bacteria. However, the narrow winning margin becomes noticeably smaller.

We must accept a new responsibility

The fact that bacteria generally develop resistances to every new antibiotic compound after some time has to be accepted as a nature-given rule. Particularly, each bacterium biosynthesizing an antibiotic indeed harbours its individual resistance mechanism to protect itself from the produced antimicrobial agent. Therefore, antibiotic production and resistance are inevitably connected to each other. The natural antibiotic producers have resistance genes which can spread from the host strain to the environment. Furthermore, resistances can occur from natural mutation within pathogenic cells. There are arrangements and rules which are able to decelerate resistance development and distribution. Thus, unnecessary application, therapies which are timed too short, and medical dosage which are too low have to be avoided worldwide. Such misusage fosters the selection pressure on the bacteria and thereby favours resistance development. One has to notice that not only the pathogenic bacteria are responsive to the antibiotics. The natural body bacterial flora of each human is addressed by the antibiotics as well. More than 700 g of the human body weight are mere bacteria mass; an estimated 300 to 500 different bacteria species inhabit a healthy human body. Here, resistances can also emerge and be transferred to other bacteria. In the year 2000, more than 160 million medical prescriptions of antibiotics have been made, that corresponds to 23 000 000 kg of active agent! Many million tons of antibiotics have to be added from intensive industrial livestock farming. Who actually wonders that this is not really working well? Antibiotics are remedies which should be applied critically and strictly medically indicated. For example, antibiotics should be only applied if the pathogens are evidence-based sensitive to a special antibiotic and only for life-threatening infections. At least of same importance is the search and discovery of novel antibiotic substances which can be brought to the market as innovative drugs. By clearly changing our attitude and our handling of antibiotics and by intensifying research, mankind could get the most out of the nature-given antibiotics. If neither the one nor the other is achieved, we will get the short end of the stick.

EXAMPLE: RESISTANCE IN HOSPITALS

Nowadays the percentage of resistant pathogens is drastically increasing, e.g., against macrolides such as the drug erythromycin. For this bacterial agent the rate of resistance is already at about 30% in Germany. Additionally, pathogens like ***Klebsiella*** and ***Pseudomonas*** – already being hard to treat – develop resistances. It takes about five years until a clinic gets rid of a multiresistant germ. Good hygiene practice and optimized therapies are the most effective counteraction. It is not affordable for clinics and the health care system to ban patients to quarantine wards.

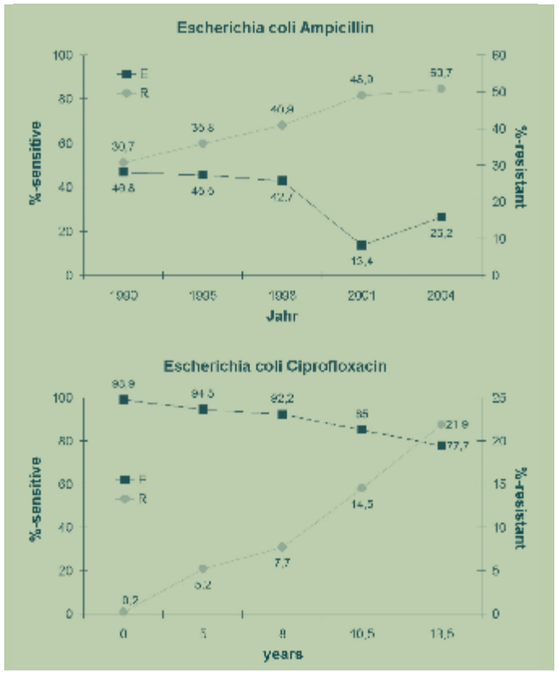
Hospital pathogens are not rare in clinics

EXAMPLE: RESISTANCE FROM POULTRY MAST

At present fluoroquinolones are applied as antibiotics in human medicine and animal mast alike. More than 43 % of all poultry salmonellae in Germany are already resistent against these antibiotics. Patients infected with salmonella cannot be treated with fluoroquinolones anymore. In the future we need world-wide obliging rules how to handle our antibiotic use. Anything less is irresponsible.

With natural product research towards new antibiotics

Using modern methods and state-of-the-art techniques of natural product research new antibiotic compounds can be discovered and innovative knowledge of the molecular modes of antibiotic action and defense mechanisms in bacterial cells can be gained. Especially in these days the pharmaceutical researchers can optimistically get to work. The latest technologies of chemical and biological analytics provides more efficiency to natural product discoveries today. By means of ***genome*** and ***proteome*** research we better understand how bacterial cells live and how we can efficiently fight them. It is generally acknowledged and proven that natural products are products of high added value with high business volumes on the market. In the last 20 years approximately half of the new low-molecular weight drugs on the market derive from natural products. Regarding the antiinfectives and the anticancer agents the percentage is even clearly higher. In rare cases new antibiotics have been obtained from chemical synthesis, for example ***linezolid***. Natural products are present in the environment for million of years and are connected with all stages of development of all organisms. The natural compounds just "fit" in the biological systems, e.g. cell constituents of humans or pathogenic germs. Therefore, optimized by ***evolution*** they are the best drug candidates to solve today's problems of missing therapeutic agents. This hypothesis is supported by the recently discovered natural



Alarming resistance development of antibiotics; data of M. Kresken, Paul-Ehrlich-Society of Chemotherapy, Rheinbach, Germany

β-Lactamase
Enzyme which deactivates β-lactam antibiotics (penicillins, cephalosporins) by alteration of the chemical structures of these antimicrobial agents.

Chinolones
Antibiotics from chemical synthesis with chemical structures deduced from natural products which inhibit enzymes of the bacterial germs concerning DNA processes (gyrases, DNA topoisomerases) and, therefore, block the cell division of bacteria. They act against gram-positive as well as gram-negative germs.

Erythromycin
Macrolide antibiotic being produced by actinomycetes strains; they inhibit growth of gram-positive bacteria due to interference with protein biosynthesis.

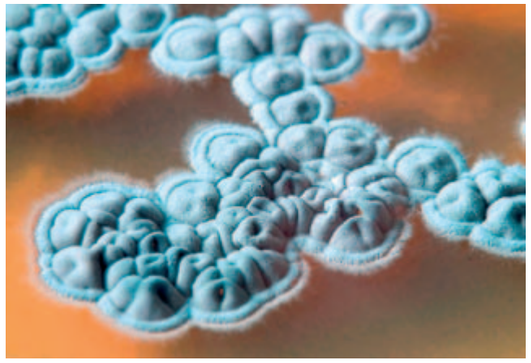
Klebsiella and Pseudomonas
Gram-negative bacteria which cause, e.g., wound infections or urinary infections.

Tetracyclines
Tetracyclic polyketide antibiotics being produced by streptomycetes strains which interfere with protein biosynthesis of gram-positive as well as gram-negative and cell-wall-deficient germs. They are used against bacterial infections either as natural products or after semi-synthetic modification. Not indicated for children due to calcium complexation.

Evolution
(lat. evolvere = evolve) Copies of a system are produced by a process of reproduction or replication. The copies are different from each other and from the original system due to variations. Only some of the copies are allowed for further copy production due to the selection process.

Genome
The total of all genetic information of a cell. For bacteria (prokaryotes) it mostly comprises a circular chromosome and additional plasmids. Eukaryotes mostly contain sets of linear chromosomes.

Proteom
The total of all proteins in a cell under certain lab or environmental conditions.



Streptomyces sp. on agar plate

product plantensimycin which has been isolated from actinomycetes strains. It is active against many resistant germs and opens-up a structurally new group of natural products. Of course, one cannot ignore that many years lie between discovering a new antibiotic structure and introducing it to the market with often more than 500 million dollars of drug development costs spent.

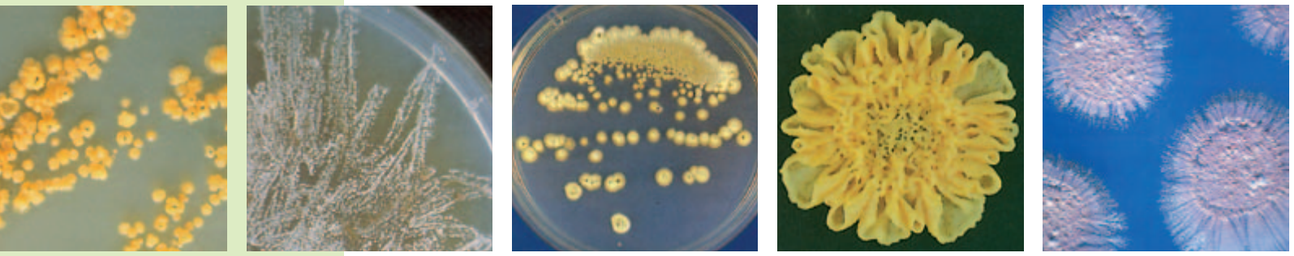
Using the treasures of nature for human medicine is a worthwhile challenge for mankind. Strikingly, there was not a single antibiotic among the 90 newly approved drugs in the US in 2002 with respect to infection diseases. In 2003, there have been two, and also in previous years only two really novel structures have been discovered for antibiotic chemotherapy with the agents ***daptomycin*** and ***linezolid***. This is indeed thought-provoking, especially since we see big pharmaceutical companies shutting down their natural products research and investigations of new antiinfectives. Surely, such decisions are market driven and depend on selling considerations. On the other hand, smaller biotech companies might be more effective and more target-oriented in developing new antiinfective compounds today. However, to realize this strategy the small companies need broad support, especially from the big pharmaceutical industry ('big pharma').

In recent years we have truly underestimated the bacteria, in particular the pathogens among them. We now realize that they are, again, an ever increasing threat. Optimized therapeutic schemes in the field of antibiotics and novel research results are necessary to control the situation currently and in the future. There is no doubt: We only have a chance with new natural products which are active against today's resistant pathogens.

Stephanie Grond and Axel Zeeck

Daptomycin
Lipopeptide antibiotic being produced by streptomycetes; active against gram positive and several multiresistant pathogenic strains. Binds to the cell membrane and inhibits the ionic distribution.

Linezolid
Member of a class of synthetic oxazolidinone antibiotics. Linezolid is mainly active against gram positive pathogens and inhibits the bacterial protein biosynthesis.



Different actinomycetes on agar plates

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Links on the Web

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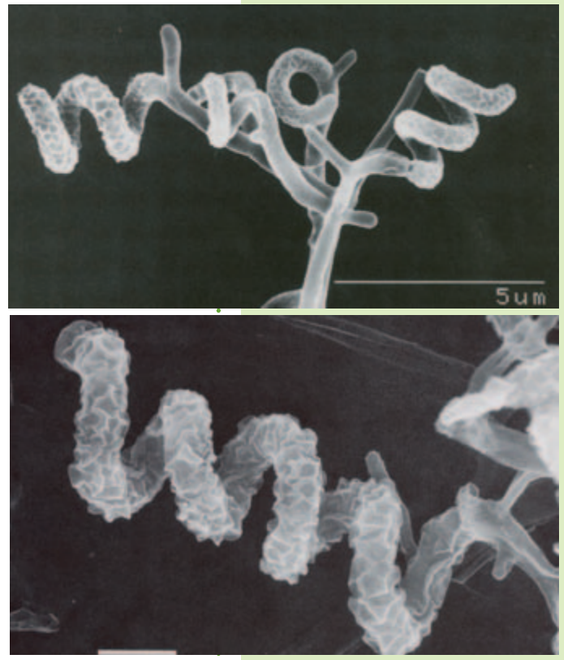
www.who.int/mediacentre/factsheets/fs194/en

National Electronic Library of Infection, Bugs and Drugs on the Web
www.antibioticresistance.org.uk

US Food and Drug Administration, Antimicrobial resistance
www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/default.htm



Streptomyces hygroscopicus (above) and ***Streptomyces plicatospous*** (below) in electron microscope.