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Microbiogical sciences: a European perspective*

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Resum. Les ciències microbiològiques, que semblava que després del descobriment dels antibiòtics haguessin quedat obsoletes, es troben ara entre les ciències biològiques més importants. Aquest ressorgiment de la microbiologia es deu en gran part a l'emergència i ràpida propagació de la resistència als antibiòtics. El fet que molts dels bacteris patogènics siguin ara resistents a la majoria dels antibiòtics dóna lloc a la necessitat crítica i urgent d'entendre les bases de la virulència bacteriana per poder tractar i prevenir les malalties. Una altra millora important ha estat la disponibilitat de tecnologies de genòmica i bases de dades que permeten explorar una gran diversitat de genomes bacterians i utilitzar-los per a interessants desenvolupaments tecnològics. Aquests dos aspectes de la microbiologia moderna seran discutits amb èmfasi a la perspectiva Europea. També es descriuran el desenvolupament i les activitats de la Federació Europea de Societats Microbiològiques (FEMS), a la qual ara s'uneixen els esforços de 47 societats microbiològiques.

Paraules clau: microbiologia europea · emergència de la resistència a antibiòtics · FEMS

Abstract. Microbiological sciences, which appeared to be obsolete after the discovery of antibiotics, are now ranked among the most important biological sciences. The revival of microbiology has been due mainly to the emergence and rapid spread of antibiotic resistance. The fact that many pathogenic bacteria are now resistant to most of the antibiotics currently in use has resulted in a critical and urgent need to understand the basis of bacterial virulence in order to prevent and treat the respective diseases. Another important development has been the availability of genomic technologies and databases, which have made it possible to explore the vast biodiversity of bacterial genomes and to use the information for biotechnological applications. This article discusses these two aspects of modern microbiology, with special focus on the European perspective. In addition, the development and activities of the Federation of European Microbiological Societies (FEMS), which unites the efforts of 47 microbiological societies, is described.

Keywords: European microbiology · emergence of antibiotics resistance · FEMS

Federation of European Microbiology Societies

The Federation of European Microbiological Societies (FEMS) links 47 microbiology societies in 36 European countries. Altogether, this means that FEMS represents over 30,000 microbiologists throughout Europe (Figure 1). The general goal of FEMS is to advance the science of microbiology and to establish a community of European microbiologists. By crossing both geographical borders within the European area and subdisciplinary borders within the field of microbiology, FEMS aims to focus on research and education, to facilitate communication (publications, congresses), and to support and encourage, for example, by awarding grants, fellowships, etc. FEMS is also the voice of microbiologists on issues relevant to the general public as well as to governmental and corporate organizations.

FEMS is a charity, registered in the UK, and its activities involve mainly publications and the support of microbiologists in European countries. FEMS publishes five journals, which cover most of the areas of microbiology, and all of them with online submission:

- *FEMS Microbiology Letters* is a unique journal aimed at the rapid publication of short research papers.
- *FEMS Microbiology Ecology* is dedicated to environmental microbiology and microbial ecology.
- *FEMS Microbiology Immunology* focuses on medical-immunological issues and bacteria-host interactions.
- *FEMS Yeasts* consists of papers dealing with the physiology, biochemistry, and genetics of yeasts.
- *FEMS Microbiological Reviews* is a very high-impact journal containing reviews on important and up to date issues of microbiology.

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Fig. 1. Logo of the Federation of European Microbiological Societies (FEMS).

The journals provide the economic basis for most of the activities of FEMS, including the support of short-term research fellowships (up to 3 months) and advanced long-term fellowships (up to one year) (Figure 2). There is also support for established scientists in the form of visiting scientists' grants. Altogether, about 50 fellowships are granted each year. FEMS also supports meetings, laboratory workshops, and working groups. These working groups consist of experts on special issues or specific topics. For example, a group on Microbiological Education, headed by Dr. Janet Hirst of the UK, has been working for several years and has organized several workshops.

FEMS also gives special awards. A young scientist award was initiated by Prof. John Norris in honor of his tutor Dr. Hans Jensen, the Danish soil microbiologist. It is given to young scientists with outstanding academic potential and achievements and is designed to help them establish their career. The grant supports at least 6 months of research and was given for the first time in 2005 to Dr. María Luisa del Río-González, from Spain. The FEMS-Lwoff prize, in honor of the French microbiologist Andre Lwoff, is for outstanding achievements in microbiological research. It was most recently (2009) given to Karl-Heinz Schleifer (Germany).

Other important activities of FEMS are the tri-annual congresses. These are pan-European, bringing eastern and western microbiologists together; they are also pan-microbiological, covering all major fields in microbiology. Thus, the congresses promote the sharing knowledge and the bridging of disciplines, with the broader goal of enhancing a transdisciplinary, pan-European exchange of information and know-how. The first congress took place in Ljubljana (2003), the second in Madrid (2006), and the third in Gothenburg (2009).

What is microbiology?

Microbiology is the study of microorganisms, a group that consists of bacteria, viruses, archaea, and small free-living cells (eukaryotes). The smallest microorganisms are the viruses. These are obligatory parasites and can only multiply inside other cells. Their size is <0.1 µm and they can be seen only by electron microscopy. Examples of viruses are the smallpox virus, responsible for large and terrible epidemics until it was eradicated by effective world-wide vaccination, and the poliovirus (30 nm , 1/1000 the size of yeasts), which, likewise, due to an effective vaccination system has been reduced from a formerly widespread disease to one with only a very small number of cases. Recently emerging and dangerous viruses that currently pose a significant potential threat to human populations are the coronavirus responsible for SARDS and the influenza A subtypes responsible for the recent outbreaks of bird and swine flu in humans.

The small free-living unicellular eukaryotes are ≥20 µm or larger and include yeasts, which are used to make bread, beer, and wines, and many pathogens, such as *Amoeba* and *Plasmodium*, the latter being the causative agent of malaria.

Bacteria are microorganisms 1–10 µm in size. Most bacteria are environmental and not associated with animal hosts. As discussed elsewhere in this volume [See article by Guerrero and Berlanga in this issue, pp. 55-61], their role is of extreme importance, as they are responsible for numerous critical processes not only for the sustainability of our planet but also for humans themselves, e.g., in digestion. Recent findings indicate

Fig. 2. Journals published by the FEMS.

that the bacteria we know represent <1% of those inhabiting the planet. Clearly, there is still much to discover and learn about environmental bacteria and their effects on Earth.

Bacteria involved in infectious diseases

Many bacteria are pathogens; in other words, they cause diseases in humans, animals, and plants. Some of these pathogens have proven to be extremely virulent. In the 14th century, the population of Europe was almost wiped out by the plague, a bacterial disease known as the Black Death and caused by infection with *Yersinia pestis*. This and similar epidemics changed the history of Europe. For example, during that time, Siena was a powerful and prosperous city, located at the crossroads between Italy and the rest of Europe. The large cathedral, the *Duomo*, was built in Siena around 1200 and enlargement of the building, including the construction of a new nave, was begun in 1339. However, the renovation was brought to a halt by the plague, which in 1348 wiped out a large fraction of the city's population. Siena never recovered its former wealth and prominence. The *Facciatone* ("big façade") still stands as a monument to the epidemic of the Black Death. Other terrible diseases caused by bacteria include syphilis and gonorrhea, typhoid fever, and cholera. After the Middle Ages, detailed records were kept about outbreaks of infectious diseases and epidemics. For example, there is a detailed record of a cholera epidemic in Exeter, UK, in 1832. In that year, the population of the city was 28,285. In July, there were 1,135 cases of cholera, resulting in 402 deaths, whereas at the same time there were only 128 deaths from all other causes.

The first scientific revolution : the discovery of the microscope and the birth of European microbiology

The invention of the microscope in the mid-17th century, by Robert Hooke, in England, and Antony van Leeuwenhoek, in Holland, gave birth to the field of microbiology and was essential to the revolutionary work of Louis Pasteur (~1850) and Robert Koch (~1900). Thus, the roots of microbiology, as a field of study, are in Europe. What did these early microbiologists do? They learned to grow bacteria in the laboratory and thus to isolate them; they examined these isolates using the newly invented microscopes; and they characterized their physiology and chemistry while at the same time developing the methods to do so. These efforts quickly led to the realization that bacteria could cause disease and to the association of specific bacteria with specific diseases. The great German microbiologist, Robert Koch—the first microbiologist to receive the Nobel Prize for Medicine or Physiology—developed the famous Koch's postulates, which must be fulfilled to define an organism as a cause of a specific disease:

- The microorganism must be found in abundance in the sick but not the healthy animal.
- The microorganism must be isolated from a diseased organism and grown in pure culture.
- The microorganism, when used to infect a healthy animal, should cause the disease.
- The microorganism must be re-isolated from the inoculated, diseased animal and identified as being identical to the original infectious agent.

These were the first steps in understanding infectious diseases and they enabled the development of anti-bacterial treatments, mainly vaccines. Some of the vaccines of the 19th and 20th centuries are effective, such as those for small pox, diphtheria, and tetanus. However, it was the development of antibiotics that marked the second revolution in microbiology.

The second revolution: antibacterial drugs

The world's first specific anti-bacterial drugs were developed in the 1930s in Nazi Germany. The man most responsible was the scientist Gerhard Domagk, who while working for Bayer developed sulphanilamide and its derivatives for use as antibiotics. This discovery earned him the Nobel Prize (although Hitler forbade him from accepting it). In 1928, Alexander Fleming discovered penicillin. This was the first antibiotic to be recognized and it paved the way for the development of many others that were and continue to be very effective in combating bacterial diseases.

As a consequence of the discovery of antibiotics, many bacterial infectious diseases, such as typhoid fever, dysentery, cholera, plague, syphilis, gonorrhea, scarlet fever, and tuberculosis, have been practically wiped out and the incidence of many others has been substantially reduced. The changes brought about by the discovery of antibiotics were immediately recorded as a significant reduction in mortality, especially of newborns and children, and in a parallel increase in life expectancy.

With the discovery of antibiotics and reduction in infectious diseases, it appeared that microbiology was becoming obsolete. However, this was in no way the case. Much to the contrary, microbiology took on an exciting, new direction—molecular biology and molecular genetics. It was soon realized that bacteria are excellent model systems for understanding biochemical processes and for learning how genes work. Indeed, bacterial research led to an understanding of the genetic code, protein synthesis, and the associated regulatory systems. And, it was research on bacteria that led to the development of genetic engineering.

The third revolution: the sequencing of a complete genome

In 1995, the first complete bacterial genome, that of *Haemophilus influenza*, was sequenced. The technological know-how for this work was developed in bacteria and it led to the ability to sequence other genomes, including the human genome, in

2001. Why is this important? What can we do with sequences of bacterial genomes? The availability of bacterial genome sequences facilitates the understanding of the basic biochemical and physiological processes of life. Most of these are similar in all organisms; thus, we can learn from bacteria about other forms of life. Genome sequences also help us to understand the basis of bacterial pathogenesis. This knowledge is essential to further combat microbial pathogens. Last, but not least, genomics is very important for biotechnological uses, in industry and in the preservation of the environment. Microorganisms are also the source of a seemingly endless amount of interesting products, such as vitamins, amino acids, and antibiotics. Bacteria growing at very high temperatures, such as in hydrothermal vents, produce enzymes that are resistant to high temperatures and can be used for in food production, in household products, etc.

Genetic engineering has enabled the use of bacteria for the production of proteins such as insulin and for viral vaccines (hepatitis, etc). Bacterial production of human insulin avoids the problems that have arisen with insulin obtained from cows or pigs, and the same is true for many other human proteins, enzymes, and hormones.

In recent years, there has been an increasing use of bacteria for combating pollution. Bacteria are very efficient in degrading toxic substances and can be used to bioremediate oil pollution or to remove heavy metals from the environment. Lately, they are being studied and tested for applications in alternative energy production. Clearly, this is a rapidly developing direction for microbiology in the 21st century.

The comeback of infectious diseases

Over the last several decades, there has been a clear increase in the occurrence of infectious diseases, accompanied by a significant rise in related deaths (Table 1).

The main reason for the comeback of infectious diseases is the development of resistance in pathogenic microorganisms. Bacteria have become resistant to most—or even all—of the antibiotics used, and the same is true for parasites, such as the one that causes malaria. Clearly, there are also new emerging diseases, such as the immunodeficiency syndrome AIDS, which is caused by the human immunodeficiency virus (HIV). However, it should be noted that people with AIDS usually die from bacterial infections that cannot be successfully treated because not only is the patient severely immunocompromised but the bacteria are resistant to the antibiotics.

Table 1. Worldwide mortality, 2002 (full report available at http://www.who.int/whr/2002/en/whr02_en.pdf)

Cause of death	%
Infectious diseases	26
Injuries	9
Maternal and birth	5
Nutritional	1
Non-communicable diseases	59

How do bacteria become resistant to antibiotics and why does resistance increase?

Microorganisms become resistant to the antibiotics because of mutations in the bacterial genome or by the acquisition of genes conferring antibiotic resistance. Mutations leading to resistance can take the form of alterations in the bacterial envelope, such that the entry of one or more types of antibiotics is prevented. Alternatively, mutations can alter the bacterial target of the antibiotic. For example, a mutation in the gene coding for an enzyme targeted by an antibiotic may change the enzyme such that it is no longer recognized—and thus no longer susceptible—to the antibiotic (see the article by Kolter, this issue).

The genes encoding resistance enzymes are often present on mobile genetic elements that can be transferred from one bacterium to another. Resistance enzymes inactivate antibiotics, rendering them ineffective. These enzymes evolved mostly in soil bacteria that have been in contact for millions of years with antibiotic-producing fungi. However, their expression in pathogenic bacteria rapidly promotes the development of a resistant population.

If, as noted above, antibiotic resistance is not new but has evolved for millions of years in nature, why, then, has it only recently become a problem? The answer is very clear—the extensive use of antibiotics has created conditions for the selection of antibiotic-resistant bacteria. When antibiotics are administered to an infected animal, all the bacteria die, except those which, through mutation or acquisition of the appropriate genes, are resistant. Where then are antibiotics extensively used? In agriculture, to treat farm animals, such as chickens, cows, and pigs, for therapeutic but mostly for non-therapeutic purposes. And, of course, antibiotics are used to treat sick people. Thus, the worst situation is in hospitals, where there is intense and widespread use of many antibiotics. The result is that hospitalized patients are at high risk of infection with antibiotic-resistant strains of bacteria.

In the USA, recent statistical studies by the Center of Disease Control (CDC) have shown that, each year, nearly 2 million patients become infected while in the hospital. About 90,000 of those patients die as a result of their infection. This is an incredible increase from the 13,300 patient deaths in 1992. The result correlates well with the discovery that more than 70% of the bacteria causing hospital-acquired infections are resistant to at least one of the antibiotics used to treat them.

What are the emerging, drug-resistant pathogens?

The list of emerging drug-resistant pathogens includes a large variety of bacterial strains and species, including several known to causes human diseases. An example is *Streptococcus pneu-*

monia, the major cause of bacterial pneumonia. In the USA, *S. pneumonia* causes 3000 cases of meningitis, 50,000 blood infections, 100,000–150,000 hospitalizations for pneumonia, and 7 million middle-ear infections each year. In 1987, 0.02% of the bacteria isolated from patients were penicillin-resistant. This number skyrocketed to 30% in 1994. Another example is food poisoning due to *Salmonella*, of the 340,000 cases per year in the US, 30% involve antibiotic-resistant strains.

In addition to "traditional" pathogens, many bacteria that we call "opportunistic pathogens" have recently emerged. These are not "classical" pathogens, such as the bacteria causing plague, pneumonia, or cholera. Rather, because of their high resistance to antibiotics and their prevalence in human environments, they have become a very major cause of disease, especially in hospitals and institutions housing the ill or the elderly. One example is the common intestinal bacterium *Escherichia coli*. Infections with *E. coli* have become a leading cause of premature death in the elderly in industrialized countries. Another example is enterococcal infections in intensive care units. Enterocci are sensitive only to vancomycin, but 14% of the strains tested have become resistant to this antibiotic.

The problem of re-emerging pathogens

Tuberculosis (TB) is a deadly infectious disease caused by *Mycobacterium tuberculosis*. It affects the lungs but can also target the central nervous system, bones, and joints

In 2004, 14.6 million people had active TB; there were 8.9 million new cases and 1.7 million related deaths. About 12% of these involve AIDS patients. Standard treatment is with a combination of two drugs: rifampicin and isoniazid. In the year 2000, 20% of the patients were infected with *M. tuberculosis* resistant to both drugs! It should be noted that Spain is one of the European countries where TB is highly prevalent: In 2004, there were 20 cases of TB infection per population of 100,000. The total number of TB cases was 8436, and there were 1119 deaths from TB during that year. Moreover, Spain and Portugal are among the countries with the highest proportion of TB cases attributed to HIV.

The urgent challenge of microbiology

In view of these grim data it is essential to face the danger of antibiotics resistance by identifying new targets for new antibiotics and by the production of effective vaccines. If these goals are not achieved, the human race will again be subject to terrible epidemics of infectious diseases.

The role of European microbiologists

Clearly, neither the return of infectious diseases nor the increase in antibiotic resistance has by-passed Europe, and both are expected to become significant problems of the 21st century. The most obvious manifestation is that of an increase in mortality due to infectious diseases and infections caused by antibiotic-resistant organisms. People infected with these microorganisms have longer hospital stays and require treatment with second- or third-choice medicines that are less effective, more toxic, and more expensive.

Moreover, Europe—as an affluent society—also faces a problem of emerging infectious diseases in its increasingly older populations, mainly as a result of infections acquired in institutions or hospitals. With the longer life expectancy of the population, these infectious diseases result in high economic costs and a large burden on the medical system. Hospital-acquired infections are a leading cause of illness and death in Europe and in the USA. In these countries the rate of hospital-acquired infections has increased 36% in the past 20 years. The annual cost of treating hospital-acquired infections in the USA is approximately $4.5 billion a year.

The important question is whether microbiology in Europe is ready for the challenge. What is the state of microbiology in Europe? Is it receiving sufficient support in terms of resources and manpower? Clearly, it is difficult to answer these questions. One fact is clear, however: Europe lags behind the USA. Microbiology started in Europe, and in the beginning of the 20th century most of the important microbiologists were in Europe. Now the situation is far from satisfactory, as evidenced by a quick glance at the list of Nobel Prize laureates. Until 1950, all the Nobel Prizes in Medicine or Physiology went to Europeans (10/10). After 1950, the situation completely changed such that between 1950 and 2007 scientists in European countries received only 16% of the prizes (6/36). The rest of them went to non-European countries.

Conclusions

The 21st century poses significant challenges for microbiology. There are important areas for biotechnological development and there is an urgent need to combat emerging infectious diseases and antibiotic resistance. Human and financial resources must be mobilized and good scientists attracted to the field. Only through these and similar steps will European microbiological sciences be able to meet the needs of European society and contribute their share in the global war for improving human life.

About the author

Eliora Z. Ron is a Professor of Microbiology at the University of Tel Aviv, where she holds the Manja and Morris Leigh Chair for Biotechnology and Biophysics. She obtained a MSc *cum laude* from the Hebrew University of Jerusalem (Israel) and a Ph.D. from Harvard University (Cambridge, Massachusetts), under the supervision of Professor Bernard D. Davis. She is the author of more than 150 publications, including

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