ESC MID
ESC MID European Council 2001 Minutes

Features
In Response to Recent Events: Update on Bacillus anthracis

Features
The Threat of West Nile Virus

Features
Infections in Pictorial Art
West Nile (WN) virus is a member of the family of flaviviruses, which also includes, among others, the causative agents of St. Louis encephalitis, dengue and yellow fever. It shares with these a common size (40-60nm), the symmetry (icosahedral nucleocapsid), the type and size of nucleic acid (positive-sense, single stranded RNA with approximately 10,000–11,000 bases) and the appearance in the electron microscope. The image shows WN virus isolated from a bovine brain.

West Nile virus causes West Nile encephalitis, an inflammation of the brain. It has commonly been found in humans as well as birds and other vertebrates in Africa, West Asia, the Middle East and Eastern Europe. 1999 marked the initial documentation of the virus in the Western Hemisphere. It is now considered permanently established in North America. The exact origin of the U.S. virus is not known, but it shows a close genetic relation to strains found in the Middle East.

The principal way of transmission is via Culex species mosquitoes, but WN virus can also be passed on by Aedes, Anopheles, and other species. In humans the virus usually remains asymptomatic or produces mild febrile disease. After a 3- to 15-day incubation period, symptoms such as fever, headache, general body ache, and sometimes skin rashes and swollen lymph glands may occur. In more severe cases (approximately 1% of all infections) patients also experience disorientation, stupor, tremors, convulsions, paralysis and coma. In rare instances, infection results in patients’ death. Case-fatality rates among those with severe illness range between 3% and 15% and are highest among the elderly. There is no therapy for WN encephalitis beyond supportive treatment.

Dear Colleagues,

The third issue of the revised ESCMID News is now in your hands. Many members have contacted me about the revised editions of our newsletter and told me that they are very pleased with the content. The Editorial Team hopes that you will continue to support and send manuscripts to ESCMID News. Our Society plays an important role in the professional and scientific European Community, also with regard to providing information and education about bioterrorism. The present ESCMID News therefore includes several articles dealing with different aspects of bioterrorism. At the successful 11th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), the European Council discussed several important topics for the future of our Society, and the minutes of the European Council meeting are available in this issue. The presentation of the ESCMID Study Groups continues in this issue with a portrait of the European Study Group on Epidemiological Markers (ESGEM). Also featured is an overview and discussion of reactions to the recent publication of the human genome. Postgraduate courses are important activities of ESCMID and the announcements for the 18th and the 19th course can be found in this issue. Infections are constant threats to human existence, which is obvious during these days. However, throughout history artists have produced visual representations of disease and human experiences of illness, including infectious diseases such as plague, smallpox, tuberculosis, malaria and AIDS. In a review article on Infections in Pictorial Art, many famous paintings in Western Art are presented. The West Nile virus causing encephalitis is transmitted by mosquitoes and now also occurs in the USA. It may appear in Europe as discussed in one of this issue’s feature articles. ESCMID is continuously supporting research in microbiology and infectious diseases by means of awards and fellowships for young colleagues, and some of these are announced in this ESCMID News. A news roundup and a list of forthcoming events in microbiology and infectious diseases conclude this newsletter. The Editorial Team wishes all ESCMID members and ESCMID News readers a successful New Year.
Message from the President

Dear Colleagues

You will receive this edition of ESCMID News as the New Year approaches. In addition to offering you my Season’s Greetings and every good wish for the New Year, it is also a time for reflection and redirection. Whilst time is a great healer, the world remains numbed by the events of 11 September and fearful for the future. Shortly after the events in Washington and New York, I put a set of proposals to our Executive Committee, indicating the way in which this Society might support its membership as well as the wider professional and scientific community in response to the threat from bioterrorism. There was swift and unanimous endorsement for a four-point approach. Firstly, we will be developing a high profile symposium on bioterrorism at the forthcoming 12th ECCMID in Milan. Secondly, we are working with the Spanish Government, who will hold the Presidency of the European Union in 2002, to develop a conference on bioterrorism that involves governments, their relevant agencies and healthcare professionals and scientists, with the goal of catalysing an effective response to this new problem. Thirdly, we will be commissioning a number of articles for Clinical Microbiology and Infection which will focus not only on describing the current threats but also provide practical guidance on the response from professionals and scientists in the areas of microbiology, infectious diseases and public health medicine. Finally, we have agreed to establish a Study Group to review and advise on the subject in an ongoing manner, and we will make its deliberations available electronically through our website and in published format. We shall be seeking the co-operation of agencies in Europe and beyond, to ensure that we effectively address this new microbiological threat.

With regard to other matters I am pleased to inform you that the Society is rapidly moving forward over a wide portfolio of activities. Some of these I will highlight briefly. Others are presented in this Newsletter. We now have firm links with several other major international organisations such as ASM, IDSA, ISID, ISC, FEMS and NCCLS. This is important since it opens the possibility of building collaborations in many areas of importance to our membership. The Society puts great emphasis on its educational outputs, and with the formation of a new Educational Advisory Committee, under the chairmanship of Claude Carbon, I can assure you that the range of activities will be increasing in quality and number. The concept of a European Summer School for specialist trainees in microbiology and infectious diseases is under development and sounds very exciting. It will also compliment our increased involvement in UEMS affairs. The Society’s journal, Clinical Microbiology and Infection, has produced some outstanding editions under the leadership of Professor Emilio Bouza and his team. The Executive is listening carefully to advice from the Publications Committee, which continues to debate the pros and cons of electronic publication. A decision is likely to be announced shortly.

Under the skilful guidance of President-elect Professor Marc Struelens and Professor Regine Hakenbeck, Scientific Affairs Officer, the ever increasing number of Study Groups continue their important work, and their outputs are now regularly seen and heard at the annual ECCMID. This is a major undertaking, but it emphasises the strength and breadth of the Society. This brings me to the issue of co-operation between European scientific societies. Significant progress has been made through a series of meetings with the International Society of Chemotherapy and its European branch (FESCI). I remain optimistic that a blueprint for developing a single annual European congress will emerge. I shall be speaking on this issue at the forthcoming 12th ECCMID in Milan, once our task force has completed discussions with all organisations responsible for regular European congresses. We all recognise that duplication of congresses is no longer appropriate since it creates competition for delegate attendance and financial support as well as dilutes the scientific quality of these meetings, all of which can only frustrate the goal of creating a single world class congress in Europe. In closing, I wish to thank all members of our Executive Committee for their hard work over the last year. Also thanks to our supporting team in Basel and Munich. A particular word of thanks is appropriate to Dr Peter Schoch, who has unlocked the potential of the Society to move forward on a very broad front. In wishing you all the best for 2002, could I also ask you to take your responsibilities as a member of this Society seriously by passing this Newsletter to colleagues and encouraging them to join our Society.

Best wishes

Roger Finch
President, ESCMID
ESC MID European Council 2001 Minutes

MEETING DURING 11th ECCMID 2001
ISTANBUL, APRIL 2, 2001

1 WELCOME AND PRESIDENT’S ADDRESS
Carl Erik Nord welcomed the members of the European Council to the 2001 meeting. A total of 89 elected country representatives, representatives from the associated specialist societies and study group / working party chairpersons were invited, 43 thereof attended. He referred to the Final 11th ECCMID Programme and the ESCMID News 1-2001 that contained both a summary of the many activities ongoing at ESCMID. Those interested in a full report on these activities should attend the Assembly of Members on April 3, 2001. The President then reminded the participants that the European Council is an advisory body to the ESCMID Executive for the discussion of issues of importance to ESCMID and the wider community of Clinical Microbiology and Infectious Disease Specialists across Europe.

2 AFFILIATED MEMBER-SHIP TO ESCMID
Peter Schoch summarised the status of the affiliation programme which is currently in its first pilot year with BIS (British Infection Society) and SSID (Swiss Society of Infectious Diseases). The objective of the programme is to provide a larger platform to both partners: for ESCMID to reach out to the many specialists not being organised at the European level, for the national societies to reach out beyond their national borders across Europe. The experiences of the pilot year will be evaluated at the end of 2002 before affiliation is offered more widely to other national societies. At present, affiliated societies pay EUR 5 per year per member. As a result of this low price only a reduced membership package can be offered in comparison to the regular ESCMID membership services. Comment by Martin Wood, UK: Through affiliation ESCMID risks to lose its regular members. It is thus important to think about additional benefits.

Question from Hilary Humphreys, Ireland: What were the criteria for the selection of the pilot societies? Answer: Initially four societies were offered to join the pilot programme: two infectious disease societies, a microbiology society and a mixed infectious disease / clinical microbiology society. They were of different sizes and came from different regions in Europe. Of these only BIS and SSID remained. The evaluation of the pilot programme will be discussed in the European Council to provide full transparency. Afterwards, we hope to offer affiliation to all societies represented in the European Council.

3 ESCMID AND THE DEVELOPMENT OF THE SPECIALTIES OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASE IN EUROPE
According to Roger Finch the many unmet needs of the specialists in the infection disciplines across Europe are also a challenge to ESCMID. The Society seeks therefore a closer collaboration with the UEMS Specialist Sections for Infectious Diseases and for Medical Biopathology. The issues of greatest importance are the recognition of Infectious Diseases as a medical speciality in those countries where this is still not the case, the specialty status of Clinical Microbiology in general, medical training and Continuous Medical Education. Regarding the latter a common project with the UEMS Specialist Section for Infectious Diseases on the development of an accreditation board is in progress. ESCMID cannot approach national authorities directly. It has therefore linked with UEMS and offers its support to help advance these professional issues at a European level.

During the discussion Daniela Marchetti, Italy, expressed her support of these goals, especially regarding an improvement of the ill-defined status of Clinical Microbiology. Niels Frimodt-Moller, Denmark, and other members were of the opinion that Clinical Microbiology should be separated from Medical Biopathology and eventually be a distinct specialty on its own. Jennifer Best, UK, asked whether ESCMID is also seeking collaboration with ECLM (European Confederation of Laboratory Medicine). Carl Erik Nord answered that ESCMID already is an active member of this organisation.

4 CO-OOPERATION WITH OTHER EUROPEAN SOCIETIES
Roger Finch alluded to the general opinion in the scientific community that there are too many European meetings in the infection disciplines. They are too expensive, too much time is invested in their organisation, and their quality is often less than optimal. To improve the situation exploratory talks with Jean-Claude Pechère, President-elect of ISC, took place. These talks have resulted in a consensus paper published in ESCMID News 1-2001 which clearly recommended that a process of convergence be established towards a single annual European congress covering the fields of Clinical Microbiology and Infectious Diseases. Follow-up talks with representatives of ISC and FESCI are planned. Several people in the audience supported this development and expressed their wish for a single world congress in Europe.

5 OTHER BUSINESS
Questions from the audience

1 Accreditation of international conferences for CME should be improved.
Can ESCMID do something about this? Answer: Yes, ESCMID is part of a project led by the UEMS Specialist Section of Infectious Diseases to establish a European Board of Accreditation of CME activities in the field of Infectious Diseases (EBAID). This board will be linked to EACCMIE which is responsible for European accreditation. A similar project might soon be started by the UEMS Specialist Section of Medical Biopathology.

2 Can the availability of travel grants for the attendance of ECCMID be improved? Answer: This is a matter of funds. This year we waived 40 registration fees and paid 20 attendance grants (EUR 500) to young European delegates. In future years we might increase this number. But the receipt of a grant will remain conditional on the acceptance of an excellent abstract.

The meeting adjourned at 13:45 h.
The purpose of this Study Group is to study typing systems used for epidemiological purposes. The group was set up informally in the early 1990s and was formalised in 1995 under its first chair Professor Marc Struelens. The current chair is Dr Lenie Dijkshoorn from the Department of Infectious Diseases, Leiden University Medical Center. The Study Group has grown rapidly, and now includes over 80 members from 20 countries.

The Study Group has a website, which can be accessed from the ESCMID website (www.escmid.org). Full details of past activities of the Study Group can be found there as well as future plans. The annual reports of ESGEM are also to be found on the website.

With the inexorable spread of resistance, the need for epidemiological typing has become even greater than it was previously. It is now seen as an essential component of clinical and public health service laboratories. The explosive growth in genomic and analytical methods over the past decade has created great opportunities in this field, but it has also highlighted the necessity for international co-operation so that methods can be optimised and used efficiently between countries and laboratories.

Like all Study Groups, membership of ESGEM is open to all ESCMID members with an active involvement and interest in the area, in this case typing systems. An effort is made to ensure that there is a balance between members involved in public health reference laboratories and those in university or research-based laboratories.

This has been successful, as currently the membership is satisfyingly broad and includes medical microbiologists, biologically orientated microbiologists and epidemiologists from hospitals, public health laboratories, universities and research laboratories. Much of the early work of ESGEM has concentrated on nosocomial pathogens, although community acquired infections are also of interest.

The aims of ESGEM are to provide a forum for members to meet and exchange ideas. Discussion of the appropriate use of epidemiological typing systems is of prime importance as is consideration of the standardising of methods across laboratories and countries. Research collaboration is an essential part of this, especially since new genomic methods are constantly being developed. Partnership with companies involved with biotechnology and in vitro diagnostics is to be encouraged.

ESGEM has been active in organising a number of meetings, workshops and multicentre studies. Like other ESCMID Study Groups, ESGEM holds meetings at each ECCMID. At the most recent ECCMID in Istanbul a symposium entitled “Typing in community acquired infections: Lessons from the prevention and control of foodborne infections” was held.

Key publications from ESGEM include a paper published in Clinical Microbiology and Infection in 1996 [1] on one of the fundamental aims of the Study Group, namely guidelines for the use and evaluation of typing methods. This paper was the result of a working party set up by ESGEM to address this important issue. Initially, the emphasis was on typing methods for Staphylococcus aureus and ESGEM organised a variety of collaborative studies to evaluate and harmonise the methods used. This resulted in a paper published in the Journal of Clinical Microbiology in 1998 presenting the results of a study using pulsed field gel electrophoresis (PFGE) carried out in 12 laboratories [2]. This study revealed that PFGE could be of great value but that a number of factors needed to be controlled carefully to ensure that results were comparable between laboratories. ESGEM was able to determine the most important factors, which included the brand of equipment used, the imaging software, the running time for the gels and the pulsing conditions.

When standardised, PFGE has been found to be one of the most reliable methods, being accurate and highly discriminatory, and it is used widely in reference and hospital laboratories. It does, however, suffer from the drawbacks of being both time consuming and technically demanding. For this reason, an additional multicentre study to evaluate...
typing methods for S. aureus using repetitive-element PCR has been carried out by ESGEM and the results reported in the Journal of Clinical Microbiology in 2000 [3]. The study was carried out in 12 centres in eight countries.

PCR methods are simpler to perform and are rapid, but also have their limitations; particularly the inter-centre reproducibility and discrimination is generally found to be less than with PFGE. Repetitive-element PCR had previously shown promise in a number of single-centre studies, but the conclusions of the Study Group were that the method, although of value, was not sufficiently reproducible to replace PFGE in the interchange of data between laboratories. This illustrates the value of ESGEM in assessing methods.

Members of the group have published on the value of PFGE for investigating the clonal spread of methicillin-resistant S. aureus in four European countries (Belgium, France, Germany and The Netherlands) [4]. The technique has also been used by members of ESGEM for the DNA fingerprinting of other species, including Enterococcus faecalis and Enterococcus faecium in aminoglycoside-resistant isolates [5] and of multidrug-resistant isolates of Salmonella Blockley [6].

A more recent aim of the Study Group is to set up a library of DNA for certain organisms, for example, the Gram-negative nosocomial species which are increasingly causing infections, including Acinetobacter, Burkholderia, and Stenotrophomonas. The strength of ESGEM is the number of members from different countries, which will be especially valuable in such tasks, as it will ensure a wide spread of isolates.

A number of facts have emerged during the time ESGEM has been evaluating methods of typing, some of which can get overlooked. In attempting to reproduce a method in a different laboratory, care has to be taken to ensure that the reagents, equipment, and details of methodology are identical. It is always essential to remember that a non-resistant strain should be included as a control. Ideally, a combination of methods is required. Most of these modern genomic methods require computer assistance for data analysis to compare strains and this is a topic under review by ESGEM. Other collaborative tasks currently in hand include the interlaboratory standardisation of typing methods for Acinetobacter, S. aureus, Escherichia coli and Legionella. The genus Acinetobacter is a difficult one to identify as there are over 18 genomic species, only some of which have specific names. Several of these genomic types are difficult to distinguish using phenotypic methods, and a variety of genomic methods have been used to identify strains [7]. An example is given in the Figure of the use of PCR fingerprinting of two such strains.

Dendrogram based on PCR fingerprints of Acinetobacter strains generated with M13 and DAF4 as primers (kindly provided by Koen van der Kouwe, Leiden University Medical Center).

REFERENCES

Pamela Hunter Medical Writer
Dear ESGAP member,

Elections for the ESGAP Executive will be held at the ESGAP Annual General Meeting during the 12th EC-CMID 2002 in Milan.

All posts are up for election but to maintain some continuity any current Executive members can put themselves forward for re-election (for a second term only).

Please send your nomination(s) to me as soon as possible and definitely by the end of February so that the necessary paperwork can be prepared in good time.

The new Executive will choose the Secretary, Treasurer and President.

Also, if you are not an ESGAP member (or you are but have not received this note by e-mail) then please think about joining. We are keen to increase active membership.

I look forward to hearing from you.

Dr Ian M Gould
Honorary Secretary

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La Pallina Rossa by Roberto Rampinelli. Art exhibition in the Giorgio Cini Foundation, Venice, during the 3rd International symposium on Nosocomial Infections Today, Nov 5–8, 2000. The exhibition and publication were dedicated to ESCMID and sponsored by Pharmacia.
SATURDAY, 15 DECEMBER 2001, 18.00 – 21.00,
ROOM E451B,
MCCORMICK PLACE,
CHICAGO, USA

You are invited to join the International Forum on Antibiotic Resistance (IFAR) symposium immediately preceding the 41st International Conference on Antimicrobial Agents and Chemotherapy. This CME-accredited symposium has the support of the European Society of Clinical Microbiology and Infectious Diseases, the International Society for Infectious Diseases and the Infectious Diseases Society of America. The symposium will preview the first publication of the IFAR Group, the Global White Paper on Bacterial Resistance in Community-Acquired Respiratory Tract Infections, together with a discussion on the public health response to antimicrobial resistance in the United States by the US Centers for Disease Control and Prevention.

The Global White Paper is a direct response to the recognition that many recommendations and calls for action to combat bacterial resistance have been made in recent years, but relatively few systematic interventions have been implemented and audited. The IFAR group comprises recognized international experts from a variety of fields, including infectious diseases, microbiology, epidemiology, health economics, outcomes research, and patient advocacy. The aim of this ambitious initiative is to critically evaluate our current knowledge with a view to addressing gaps in our understanding of bacterial resistance and how it can best be controlled.

In previewing the Global White Paper, the IFAR Symposium will:

• Define the principles of good microbiologic surveillance and evaluate how surveillance data can best be interpreted and used to support strategies to control resistance.
• Critically assess our understanding of the clinical and socioeconomic impact of resistance in community-acquired RTIs.
• Review the key factors driving resistance and assess the link between resistance and antimicrobial usage.
• Explore the role of the patient in resistance spread and control, and the potential benefits of shared decision-making in this setting.
• Explain the challenges in applying our understanding of resistance to disease management and to the development of clinical decision-support systems, such as published guidelines.
• Review strategic recommendations for resistance control, explore how and where these have been translated into interventions, and highlight where these efforts have been effective.

We welcome all parties interested in moving the resistance debate forward to participate in this innovative and influential meeting.

Jointly sponsored by the Dannemiller Memorial Educational Foundation and Adelphi Communications. The IFAR and the Global White Paper have been made possible by an unrestricted educational grant from Aventis Pharma. The IFAR would like to stress that the sole focus of this initiative is the threat of antimicrobial resistance worldwide and that no commercial aspects have been considered.

Results of Free Membership Raffle

We are pleased to announce that

Dr Ergin Ciftci from Ankara, Turkey,
Dr Martin Laurell from Malmö, Sweden, and
Dr Vincenzo Cuteri from Perugia, Italy,

have won a free ESCMID membership for the year 2002. They were drawn from among those who participated in our opinion poll after the 11th ECCMID 2001 in Istanbul. Congratulations come from our ESCMID offices in Basel, Switzerland, and Munich, Germany.
We are looking forward to seeing you at the 12th European Congress of Clinical Microbiology and Infectious Diseases Milan/Italy, April 24–27, 2002

http://www.escmid.org/eccmid2002
The International Sepsis Forum (ISF) is pleased to announce a research grant of EUR 10,000 for research in the field of sepsis. The objective of this research grant is to promote research on sepsis. Appropriate projects may be basic science or clinically orientated, or a combination thereof.

APPLICATION
An Application should consist of:

• a paper not exceeding 2 pages in length (including references and figures) setting out the applicant’s previous work and a detailed research plan (application papers exceeding 2 pages will not be considered)
• a full CV
• a letter from the current Head of Department confirming that the applicant is under 40 years of age and that the applicant, if awarded, will be provided with the necessary facilities to take up the award
• the names of two referees, other than the Head of Department

Applicants must include their complete postal and e-mail address, telephone and fax numbers, as well as those of the 2 proposed referees. Members of the ISF and ESCMID Executive Committees are ineligible. No correspondence beyond that necessary for the application will be accepted.

The selection of the recipient will be made by a joint ISF/ESCMID committee, which will make a recommendation to the ISF Steering Committee. We anticipate that the successful candidate will be informed by 15 February 2002.

The Award will be presented at the 12th ECCMID 2002 in Milan during a joint symposium organised by the ISF and the ECCMID Programme Committees. The applicant should be prepared to give a 30-minute lecture about his or her research on this occasion.

For further information about the congress see: www.escmid.org/ecmcid2002.

Applications are to be submitted electronically to Prof Patrick Francioli, Programme Director of ECCMID, at Patrick.Francioli@chuc.hospvd.ch by 15 January 2002 at 12pm. Late applications will not be considered.

For other details please contact Elaine Rinicker, ISF Programme Manager, via the ISF website at www.sepsisforum.org.
September 11, 2001 will be deeply etched on all our minds in so many different images. The way we view our world has changed. One change will, without doubt, be the need for all in the infectious disease community to radically review and revise their knowledge on the issues surrounding possible bioterrorist attack. The anthrax cases in the USA and scares or hoaxes in Europe and elsewhere all underline this need. The problem as I perceive it is that there is a vast amount of information available, mainly on the web but also in professional journals. Some is of an excellent quality (for example www.who.int and the occasional series in Clinical Infectious Disease). There is a need for help in this labyrinth.

Firstly, there is the need to re-acquaint oneself with the clinical and therapeutic issues such as, for example, the early diagnosis of anthrax, its prophylaxis and need for very early treatment. We should ponder whether in a major incident we should consider NOT admitting infected patients. Difficult decisions will be required at times of great professional pressure. We need to prepare for this.

Secondly, it is important for us to ensure that colleagues in emergency services receive appropriate advice upon which they can base their major decisions. The TOPOFF exercise\(^1\) and its important lessons should be compulsory reading. The drafting of public health plans which, I feel confident, are going ahead in many European countries, must be in consultation with the infectious disease community. The central stock piling of appropriate antimicrobials and vaccines must be addressed, as must the problems of individual hoarding. The pressures on health care over the last decade have led to a paucity of hospital beds. Gone are the ‘fever hospitals’. We should ask how we could handle a significant smallpox release, for example, without ‘dedicated’ hospitals.

Thirdly, there is a major need for more rapid diagnostic methods, like DNA-based array systems. They have been developed for the military – now they should be introduced into the civilian sector.

The role of societies, such as ESCMID, where there can be full and frank exchanges of views, cannot be over-estimated. We are all under an obligation to meet these new challenges however repugnant they may be.

R. Wise
City Hospital NHS Trust
Birmingham, UK

REFERENCES
The Human Genome: Reactions

The publication of the first draft of the human genome early this year has elicited comparisons with events as diverse as the Apollo Space Program, which put men on the moon, and the Manhattan Project, which fostered the race to develop an atomic bomb. The report has been described as “the most wondrous map ever produced” as well as “a scientific indulgence”.

James D Watson acknowledged that neither he nor Francis Crick ever imagined, in 1953 when they discovered the double helix, that “the human script” would become available within their lifetimes. At that time, “just learning how cells read the genetic information within DNA seemed a tall order”, and now humans, like cells, are able to “read the messages of the genes”.

The species can now read and download from the internet its own recipe. This degree of availability and the notion of public access in general are at the heart of the politics of the project, as is the factor of competition between the public and private sectors. The publicly funded scientists who are involved in the Human Genome Project had “read” 10% of the human genome by early 1998 and predicted that they would finish in another seven years. At the same time, Celera Genomics, a company in the private sector, announced that it would complete the project by 2000, and at a fraction of the cost. Rising to the occasion, the publicly funded Consortium reorganised with additional funding, set a goal for June 2000, and Celera Genomics adjusted its own timeline accordingly. A joint announcement of the completion of the rough draft was made on 26 June 2000, and the results of the Consortium and of Celera Genomics were published, respectively in Nature and Science in mid February 2001. It cannot be ignored that the efficiency of the private venture is explained to a certain extent by its access to the sequence data made public by the Human Genome Project. This is only a partial explanation, however. The ambitious combination of the two methods of assembly employed by Celera Genomics, as opposed to the primarily map-based approach employed by the Consortium, bly come from focusing on the human homologues of genes of known functions in one or more model organisms”. However, he believes “we must move beyond the DNA script and the RNA or protein actors that carry out its instructions”. At some point, “even more important dividends will come from focusing on ourselves as human beings and making sense of the oft seemingly intractable relations between nature and nurture”. Peer Bork and Richard Copley from the European Molecular Biology Laboratory (EMBL) in Heidelberg agree that the era of rapid growth in human genomic information is over. The challenge now is “understanding how this comparatively small set of genes creates the diversity of phenomena and characteristics that we see in human life”. This, as well as finishing the project. Unlike the sequences of the human chromosomes 21 and 22, published in the Proceedings of the National Academy of Sciences in 1986, the present sequences of the entire human genome are considered a rough draft because they are not continuous. One definition of “finished” is that fewer than one base in 10,000 is incorrectly assigned, more than 95% of the euchromatic regions are sequenced, and each gap is smaller than 150 kilobases. According to these standards, which are achievable with current technology, over a quarter of the public Consortium’s sequence is considered complete.

“Each new round of press conferences announcing that the human genome has been sequenced saps the morale of those who must come to work each day actually to do what they read in the newspapers has already been done.” Maynard Olson from the University of Washington Genome Center points out that these people are left to finish the work “even as the bright lights of media attention shift elsewhere”.

For the moment, the notion of genetic diversity continues to be in the spotlight,
which has not always been the case. Mark Stoneking from the Max-Planck-Institute in Leipzig reminds us that the first study of genetic variation in human populations was published in 1919, by the Polish immunologists Ludwik and Hanka Hirsfeld, in Anthropologie after being rejected by the Lancet.

The current editor of the Lancet, Richard Horton, probably would have published the paper. However, he is among those eager to raise questions about the practical value of mapping the genome. What value exists is thought to lie precisely in the genetic variation between individuals, as indicated by the presence of single nucleotide polymorphisms (SNPs). These points of substantial variation in the DNA sequence, important because they identify genetic variation, should open the way to finding genes linked to diseases. An expectation that medical applications of the human genome would be its most significant benefit was the single most important justification for funding the project. Without a functional understanding of what genes do, however, it is not evident what the mapping of the genome will add to our understanding of disease.

Aravinda Chakravarti from the Institute of Genetic Medicine at Johns Hopkins University in Baltimore believes that studies of SNPs and disease will become more efficient only when the micro-distribution of SNPs in individual populations is known, when computational analysis provides information about the effects of (unequal) SNPs in order to understand their involvement in disease, and when the technology to assay thousands of SNPs in thousands of patients and controls is developed beyond the current stage of creative idea.

The press and the public at large are less cautious. Outside the research community, it is widely believed that simply knowing the sequence of the human genome will revolutionise medicine. The belief, in essence, is that the ability to catalogue variations within the genome will lead to the identification of genetic profiles that are prevalent in multifactorial, polygenic diseases, which will lead to early detection, treatment and prevention. Similarly, it is generally accepted that an understanding of genetic constitution which influences an individual’s susceptibility to disease, in conjunction with environmental and other factors, will lead to an understanding of why some individuals with a particular disease respond better than others to drug treatment.

Public enthusiasm and the desire to situate the moment in history are nicely illustrated in a statement by Tony Blair. “Let us be in no doubt about what we are witnessing today: a revolution in medical science whose implications far surpass even the discovery of antibiotics”. Two examples from the international press demonstrate agreement. In Spain, El Pais declares that the door has been opened to “a new era for medicine and biology, as well as for finding a cure for a large number of diseases”. The China Daily maintains that “in addition to genetic disease, the knowledge of human biochemistry that is contained in the human genome could hold new insights into tackling infectious diseases”. On the other side are the more complex issues implicit in the access to this new information about the human genome. While The Guardian takes a neutral stance in declaring the beginning of an era of a new kind of medicine that is tailored to a patient’s unique genetic makeup, The Irish Times points out that immense hope for curing diseases and eliminating birth defects has been raised, alongside the fear of genetic discrimination and selective breeding. The Namibian Times refers to a mistrust that this information will be used to create “perfect people” and voices the concern of some scientists that the achievement will benefit only those living in wealthy countries.

Among those who remain sceptical about the appropriateness of revolutionising health care according to genetic information, Richard Horton asks pointedly whether the sequence of DNA is indeed the key to life, the code of codes, or rather “a dead molecule” as Richard Lewontin once called it. Aside from the technical issues of genes interacting with external environmental factors and random events to produce disease, he argues that there is still some value in preserving a freedom to live without the “perpetually pressing knowledge that genes can be fractioned and totalled into a finite risk” of a particular disease, that an individual may be better off without knowing the disease(s) inherent in his genetic makeup. In Richard Horton’s opinion, what is really needed to understand biological and cognitive complexity is a compass rather than a map, and the “human genome project is a scientific indulgence when set beside the challenges of malnutrition, poor water systems, unsafe sex and unbridled tobacco use”.

David Baltimore from the California Institute of Technology does not speak as strongly, but he has stated that, conceptually, the recent draft “doesn’t hold a candle” to the breakthrough for which Watson and Crick are responsible. Still, in his opinion, the inevitable result of the Human Genome Project is that “biology will become an engine of transformation of our society”. Rather than guessing about how individuals differ among themselves, “we will understand and be able to tailor our life experiences to our inheritance” and, to some extent, to control that inheritance.

As one means of control, Peer Bork and Richard Coppley suggest that the information we now have could be used to exploit technologies such as chips (made using DNA or protein) to augment traditional approaches to medicine. For example, all members of a protein family could be contained in such chips, making it possible to determine which are active in diseased tissues. Finishing the sequence is crucial because each “missed gene is potentially a missed drug target”. The current collection of drugs in use is derived from fewer than 500 targets. Looking forward, the existence of a complete catalogue of genes suggests vast opportunities for drug development.

Errors in single genes are responsible for many hereditary diseases, most of which are rare, but which affect, collectively, a large proportion of the population. Then there are those diseases whose manifestations are enhanced or abetted by genes. David Ridley, author of Genome, describes the genome as a text in which is written the past history of plagues. Our ancestors’ struggles with malaria, for example, are recorded in the patterns of human genetic variation. The chances of avoiding death from malaria are pre-programmed in
an individual’s genes, and in the genes of the malaria-causing organism. However, similar to Richard Horton’s reasoning, David Ridley points out that genetic resistance to disease is the last resort. More simple measures to combat malaria include draining the swamps, sleeping under mosquito nets, and taking a pill. The inherent susceptibility to cholera is another example. In the late 1980s, it was discovered that individuals with blood type O are much more susceptible to cholera (although, by the way, more resistant to malaria). Those with blood types A, B and AB differ in degree of susceptibility to cholera, individuals with type AB being most resistant, virtually immune. Finally, the link between genetic diseases and infectious diseases has become increasingly a subject of investigation and speculation. According to some, the reasons behind genetic variability always seem to have something to do with infectious disease.

Watson and Crick’s concluding comment in 1953, “It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material”, has been repeated in part in the concluding thoughts of the Consortium’s publication in 2001, “It has not escaped our notice that the more we learn about the human genome, the more there is to explore”. Repeating that phrase once more to summarise this brief overview, it has not escaped our notice that the reactions to the sequencing of the human genome are as controversial and contradictory as is human nature as we have known it until now. One wonders who among the Consortium’s thousands of contributors had the genetic makeup that produced the impulse to conclude the report of the initial sequencing and analysis of the human genome with two lines of poetry: We shall not cease from exploration. And the end of all our exploring will be to arrive where we started, and know the place for the first time. T.S. Eliot

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**The Human Genome: Ten Surprises**

listed in order of increasing importance

The human genome is not at all homogenous as expected, but rather, is very heterogeneous. The topography is distinct from that of other organisms, with genes unevenly scattered across the genome to create a terrain consisting of dense “urban centres” as well as vast expanses of “desert”.

The human gene count is much lower than initially expected; rather than 100 000, the count is closer to 31 000, not many in light of what they actually do.

Human genes are capable of making more proteins than genes from other organisms, because of gene splicing.

Human proteins, by virtue of domains, are architecturally more complex than those from other species.

Some human genes may have been acquired from bacteria by horizontal transfer.

Repetitive sequences in the human genome provide a fossil record dating back 800 million years.

A major part of “junk” DNA appears to have an important function (some repeats are retained in gene-rich regions).

The male mutation rate is twice that of the female (i.e., males are more responsible for both genetic “mistakes” and genetic evolution).

Humans are 99.9% identical at the DNA level; thus, there is no genetic justification for racial or ethnic labels.

Our understanding is more advanced and our progress more rapid than anticipated due to public accessibility without restrictions (i.e., updates on the internet every 24 hours ensures access to anyone with an idea).

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Francis S Collins
National Institutes of Health, Bethesda
The Threat of West Nile Virus

A n observer unfamiliar with the surroundings would hardly spot the object in the thin aspen grove: a box, painted white, its base of about 2x1 meter standing on four blocks, and its cover half raised. Coming nearer, the observer would hear a characteristic cackle, and a look in the open part of the cage would confirm the suspicion that this peculiar object in the middle of the South Canadian wilderness is a chicken cage. The hens are owned by the Laboratory Center for Disease Control in Ottawa, the health authority responsible for the control of infectious diseases. The ten white hens in the mobile cage could be considered a permanent monitoring eye of the Canadian authorities. Together with several hundred more members of their species, distributed in dozens of cages along the Canada-US border, they form a “radar system” for infectious disease, specifically designed to recognise the arrival of a microbial enemy, the West Nile virus (WNV).

Once a week, blood is collected from the hens and tested by a PCR method for the presence of WNV. If viral RNA is present, this activates the next stage of a sophisticated monitoring system: the bodies of dead wild birds, mostly crows, are systematically collected and examined for the presence of WNV, and night-active mosquitoes are caught with the help of special traps and analysed as entomological pools. Veterinarians are advised to watch out for suspicious symptoms in horses, dogs, and cats. And finally, using all available media channels, the general population is informed about the impending health menace. The efforts displayed by the Canadian health authorities stem from an entirely justified concern: the first encephalitis case caused by WNV this year appeared at the end of last July in a woman living in Staten Island, New York, and the presence of the virus in various mosquito pools in this federal state is further evidence for the continuing proliferation of the virus. It has also been established that WNV has already crossed Lake Ontario - “piggyback” with the help of an American crow - and it has been detected in the bodies of 28 birds found in the Province of Ontario. But the New York health authorities too are in a state of alarm. Staten Island has been “vapourised” repeatedly with insecticides, a preventive measure to decimate the populations of the vector mosquito species Culex pipiens, Culex restuans and Culex salinarius. Meanwhile, the population was advised via the media to follow strict exposure-prevention measures and not to stay outdoors in the evening hours. The city administration has taken these drastic measures to avoid a West Nile Virus epidemic similar to the one of 1999. At that time, during the period from mid August to the end of September, 62 persons had contracted a meningoencephalitis and seven of them died. About two thirds of the diseased were elderly people.

A representative part of the population was tested for antibodies to West Nile virus in a seroprevalence study carried out in the fall of 2000, and this revealed that in the previous year 1574 persons had become infected with the virus in the borough of Staten Island alone. Of these, every 157th contracted an encephalitis. Overall, 19 patients had become sick with a WNV encephalitis in the greater New York area. In the transmission season, 317,676 mosquitoes in 9,952 pools had been tested for WNV infection – a rather Herculean task, even if the test methods were largely automated. 363 pools harboured positive results. The epidemic acquired a new dimension when, in the summer of 2000, West Nile virus was observed for the first time also in Florida.

Not only have two persons already contracted encephalitis in Northern Florida, but the virus has been detected in numerous horses and wild birds, as well as in various mosquito pools. The situation, however, was to get even worse: by the end of September, evidence of viral activity in birds or mosquitoes had been confirmed in eleven East Coast states. The virus with the unusual name (it was isolated for the first time in 1937 from a female patient in the West Nile Province of Uganda) is a member of the flavivirus group. These pathogens are transmitted exclusively by mosquitoes, and the group includes such dangerous pathogens as yellow fever virus, Japanese encephalitis virus, Murray Valley encephalitis virus, St. Louis encephalitis virus and Kunjin virus. WNV occurs not only in Africa, but also in Asia (especially in Russia), as well as in Israel and Eastern Europe. Severe epidemics have been recorded in 17 countries so far. The virus multiplies in various species of birds, some of which, e.g. the American crow (Corvus brachyrhynchos)...

**West Nile virus on our front door?**

In July 1996, West Nile virus was detected for the first time in humans on the European Continent (although there had been an outbreak in animals already in 1962 in the Camargue in the South of France). An epidemic broke out within a few weeks in Bucharest and in the lower Danube Valley and 395 persons contracted meningoencephalitis. The disease incidence was 12.4 per 100,000 inhabitants, with a seroprevalence of 4.1%. The epidemic went nearly unnoticed in Central Europe, and the badly equipped Romanian health authorities were left alone with the problem. Systematic measures to control mosquitoes and an epidemiological analysis were undertaken much too late, so that the virus was able to spread unhindered over weeks. When, at the beginning of the fall, the epidemic lost its momentum, 17 persons had paid the inefficiency of the Romanian health system with their lives. After an WNV epidemic of catastrophic scale broke out last year in Israel – 417 disease cases, 326 stationary treatments and 35 fatalities – all patients with diseases accompanied by high fever are now routinely tested for WNV. In 2001, this systematic screening has already lead to the detection of a few cases in patients treated for other diagnoses.
West Nile fever: diagnosis, clinical picture and course of disease

After an incubation period of 3 to 6 days, disease starts without any prodromal stage with fever, joint pains and headache. In about half of all cases, temporary skin alterations (skin rash) and lymph node swelling are observed. The fever abates about one week after the onset of symptoms.

As with other flaviviruses, however, a typical biphasic fever progression is observed with West Nile virus: after a few days of normal body temperature, fever increases again strongly. Cerebral complications (meningitis and encephalitis) always occur in this second fever period. It is not known why these complications are particularly frequent in the elderly. (In the age group over 65, meningoencephalitis occurs in 1 of 50 infected patients, in younger patients only in 1 of 300.) The lethality of this form of disease is between 3 and 15%. Convalescence can take weeks, and it is rare for defects to heal up. The diagnosis West Nile infection is based on the detection of specific antibodies and/or the detection of viral RNA by PCR. There are only a few reference laboratories which carry out these tests.

There is no specific treatment. Usual supportive measures are required, according to the severity of the disease.

and the house swallow (Passer domesticus), get severely sick, like humans, whereas others harbour the virus without signs of disease.

Humans, and occasionally cats and horses, get infected when ornithophile mosquitoes pick up the pathogen from a bird and later transmit it to their next victim, when sucking its blood. Human-to-human transmission has not been observed.

The fact that dangerous pathogens such as the West Nile virus may suddenly make their appearance on a previously spared continent took the American authorities completely by surprise in the summer of 1999. Within a few days, dozens of elderly people in a 10 km radius had contracted a meningoencephalitis of mysterious aetiology. At the same time, dead crows were literally falling off the sky by the dozens. And in the nearby Bronx Zoo, just 8 km North of the “epicentre” of the epidemic, rows of birds as diverse as Chilean flamingos, guano-cormorants and white-headed sea eagles died, while hastily summoned veterinarians were unable to explain what was going on. Only later did it become clear that humans as well as animals had all fallen victim to an infection with West Nile virus. Extensive insect control measures throughout the metropolitan area of New York finally brought the epidemic to a collapse at the beginning of the fall.

While, at that point, this unexpected appearance of the West Nile virus in New York could still be interpreted as a chance, or one-time, occurrence, it has now become clear that the pathogen has definitely settled in the New World. Whether further spreading of the virus and new epidemics can be avoided by means of the large-scale insect-control measures now undertaken remains to be seen. Professor Charles H. Calisher of the Department of Arthropod Borne and Infectious Diseases at Colorado State University, for one, thinks that East Coast residents are at considerable risk. According to Calisher, our entomological knowledge of the various insect vectors (several species of Culex, Ochleratus, Aedes and Anopheles mosquitoes, leading to the infection of humans with malaria parasites when bitten.) It is much more likely, however, that migratory birds have carried the virus from Asia. Ornithologists know of several species of birds who, coming from Asia, spend the winter on the East Coast of America. Indeed, there are four routes used by migratory birds over New York – one passing almost exactly over the borough of Queens, where the index cases were observed in 1999.

The almost complete genetic homology of the first isolate of WNV in New York in 1999 with isolates from Israel between 1997 and 2000 suggests that the pathogen got into the New World via Israel.

Hermann Feldmeier
Infections in Pictorial Art

Sickness and death have been themes for artists at all times. They have painted what they themselves have experienced, have seen, or have been told. Or they have themselves suffered from disease. All great epidemics have left traces in the history of art, which will be exemplified in this article. There will be examples of infections caused by gram-negative and gram-positive rods, a protozoan infection and infections caused by viruses. The selection of paintings is limited to Western art.

The plague has been one of the worst scourges of humankind. It swept over large parts of the world in huge waves. The infection probably spread slowly westwards from China along the big caravan roads. During the fourteenth century the infection spread to Europe from the Crimea. Between 1348 and 1720 there were about ten plague pandemics and twenty-five million people are believed to have died. Many artists have depicted the waste of the Black Death. One of them was the Belgian painter Pieter Breugel the Elder who, around 1556, created the famous painting “Triumph of Death” (Fig. 1) in the style of a pictorial broadsheet. Death is depicted as a mechanical professional army that passes through a town. No one can escape their fate; individual personalities like the emperor, the cardinal, a mother with her child, the pilgrims and a jester are all summoned by Death. There is a place for executions in the background, and the victims are carted to their graves in a tumbrel drawn by a bony horse. A party is interrupted. In the lower right-hand corner there is a pair of lovers playing music without recognising that they have become a trio. Death sits behind them and plays the violin.

When the French painter Nicolas Poussin wanted to depict the waste of plague in Northern Italy he used the first biblical mention of plague, which is in the first book of Samuel around 1000 BC. The Philistines had conquered the Israelites and stolen the Ark of Jahve and placed it in the temple of Dagon in Asdod. God punished them by giving them boils. They moved the Ark to another town but also their God punished them with boils. The Philistines were advised by their priests to send away the Ark and make pictures in gold of their boils and their rats. Poussin painted “The Plague at Asdod” (Fig. 2) in 1630–31. In the centre a man can be seen trying to save a small child from the dead mother. The man holds his hand to his mouth to avoid the stench from the sick and dead victims. Poussin has also painted some rats in the street, although at that time the connection between the infection and the rats was not known. The role of the rat was proved after Yersinia pestis had been identified independently as the causative agent by both the Swiss Alexandre Yersin and the Japanese Kitasato in 1894.

Cholera, like plague, is a very old infection. It was first described in India in the fifth century BC. Cholera was probably re-
stricted to India for many centuries, but from 1817 the infection started to spread throughout Asia and via Arabia and Egypt to Europe where it arrived in 1828. Several epidemics passed over Europe during the nineteenth century. The mortality was high, with 18000 people dying in 1832 in Paris in just 6 months.

The French artist Honoré Daumier has made some very sharp-sighted lithographs from the years of cholera in Paris. Daumier contributed to the French journal Charivari, where his lithographs were published for 27 years. They are a harrowing record of the cholera epidemic in Paris, made by keen observation and brilliant characterisation. One of his drawings (Fig.3) shows a street in Paris with victims of cholera, a hearse, a stretcher with a dead person, a sick man in the street, a sick dog. Robert Koch discovered the causative agent, *Vibrio cholera* in 1884.

Another very old infectious disease is leprosy. It has played an important role in peoples’ imagination and in art. The disease was prevalent in the East in ancient times. As far back as the second millennium BC, traces of leprosy can be found in exhumed corpses from China and in mummies from ancient Egypt. During the eighth to tenth century, leprosy spread to many southern European countries, and via the crusades the disease become widely distributed in Europe.

Many artists in older times have depicted patients with leprosy. The Italian painter Cosimo Roselli has painted a scene from the Sermon on the Mount (Fig.4). A leper is kneeling before Jesus Christ and entreating the Lord to relieve him of his suffering. The man’s body is full of blains typical of leprosy. The painting was made at the end of the fifteenth century and is one of the most famous paintings in the Sistine Chapel in the Vatican.

Another well-known painting is that of an anonymous artist from the school of Konrad Witz, a German painter working in Konstanz and Basel. His art was realistic and was influenced by Flemish painting. His works include several paintings for altar wings in churches in Basel and Geneva. The painting made by the anonymous artist around 1450 (Fig. 5) is from an altar wing in a church in Alsace. It depicts St Martin who at the town gate of Amiens encounters a beggar in rags, sick of leprosy. St Martin drew his sword and cut his cloak in two giving one half to the beggar. The same night Christ appeared to him dressed in the
half of the cloak he had cut off. The beggar shows some characteristic symptoms of leprosy. He has many blains. The skin in the face is thickened. The disease has caused thickening of the peripheral nerves, resulting in impaired sense of feeling. The beggar has lost the sense of feeling in his legs and is now a cripple. He moves by aid of primitive crutches. One of his feet is deformed. Mycobacterium leprae was discovered in 1873 by the Norwegian physician Armauer Hansen.

Tuberculosis is an infectious disease almost as old as humanity. It has been described in one of the earliest medical works written in China in the third millennium BC. Signs of tubercular disease of the spine have been found in a 3000-year-old mummy. Hippocrates described the disease and also some therapies. In the history of creative work there are many artists and writers who have had experience of sickness and worry or suffering exist.

The childhood of Edvard Munch was darkened by the experience of sickness and death. When he was five years old his mother died of tuberculosis and when he was fourteen years old his sister Johanna Sofia died. He himself had rheumatic fever. Hence, his art very early came to deal with sickness and death. One of his most famous pictures "The sick girl" (Fig. 7) is a touching portrait of his sister dying of tuberculosis. He often used this theme in his paintings as well as in his graphic works. Robert Koch received the Nobel Prize in 1905 for his discovery of Mycobacterium tuberculosis. Malaria is another infectious disease with a long history dating back to ancient times. It is caused by a protozoan belonging to the family Plasmodium. There are four species of Plasmodium that cause disease in humans. One of these species, Plasmodium falciparum, is believed to have existed 2.5 million years ago in Africa and South East Asia. Malaria came to Europe rather late; it spread from Greece to Italy and to the whole Mediterranean area. On a sketching tour of the Netherlands around 1520 the German artist Albrecht Dürer was stricken by malaria. For the information of his doctor, who had to make a diagnosis, he drew a self-portrait on which he is pointing to his waist noting: "The yellow spot to which my finger is pointing is where it hurts" (Fig. 8). The malaria parasite was detected in the blood of malaria patients by the French colonial officer Dr Charles Louis Laveran. He received the Nobel Prize in 1907.

Virus infections are very common, especially in the respiratory tract as a common cold. A more severe form of virus infection in the respiratory tract is influenza. Epidemics resembling influenza were mentioned long ago by Hippocrates. The name influenza was used the first time by an Italian author in the sixteenth century. Some influenza epidemics are named after the country of origin. The Russian flu was widespread during the eighteenth and nineteenth centuries. In the middle of 1918, at the end of the First World War, there was an epidemic in Europe, first officially recognised in Spain; hence the epidemic was called the Spanish flu. It spread to many countries around the world. It has been estimated that at least 20 million people died in this epidemic. The Swedish artist Hilding Linnqvist was stricken by the Spanish flu in 1920 and was admitted to Sabbatsberg hospital in Stockholm. He was very ill with a complicating brain infection. As soon as he began to feel better he set about studying the hospital environment and made the painting "Hospital ward II" (Fig. 9). It reflects the calm emotional state of convalescence. The blue in the windows interacts with the blue uniforms of the nurses as if they were ministering spirit.

Fig. 7: Edward Munch: The Sick Girl
Artwork: © Munch Museum/Munch;
Photo: © Munch Museum (Andersen/de Jong)

Fig. 8: Albrecht Dürer: The Sick Girl

Fig. 9: Hilding Linnqvist: Their capital Ward
Photo: © Moderna Museet, Stockholm

Polio was known in ancient Egypt a millennium before our era. A mummy from around 3700 BC seems to be the oldest known patient. Hippocrates reports an epidemic on the island Thasos which may have been polio. In Ireland in 707 AD an epidemic of polio is Heine-Medins disease. The Swedish artist Jusepe de
Ribera born in 1588 and living in Naples from 1616 painted Lo Storpio, the cripple, in 1642 (Fig. 10). The painting shows a boy from the poor part of Naples with lameness and contraction of the right arm, bone and foot, probably caused by polio. The artist wanted to show his sympathy with the poor people in the society and with the handicapped, so he painted the boy seen slightly from below, thus giving him a noble position emanating both pride and happiness.

Syphilis came to Europe with the return of the Conquistadors from South America and first appeared in Barcelona in 1493. The history of syphilis is full of meanings and myths. Among privileged people, the princes in the sixteenth century, the aristocrats in the eighteenth and the bourgeoisie in the nineteenth century, syphilis passed as a gallant disease. But among the poor people it was only disgusting. From the middle of the nineteenth century the control of the infection in the Nordic countries concentrated on the prostitutes. With the help of the police every woman who was suspected of being a prostitute was traced and arrested. She had to be registered and was instructed to visit an inspection office twice a week. In the presence of two policemen a doctor would then examine her. These inspections were of course degrading for the women. The Norwegian artist Christian Krohg painted a touching picture of the shy Albertine in the waiting room of the police doctor (Fig. 11), while the more experienced prostitutes are staring at her. This painting started a public debate on prostitution in Norway. At the end of the 1890s Edvard Munch made the picture “Heritage” (Fig. 12), which is a frightening illustration of syphilis. The woman carries on her knees a pale child with a rash over the trunk, a symptom of inherited syphilis. Great attention was drawn to this painting at the “Salon des inependants” in Paris in 1902. But many visitors did not understand the painting and laughed at it. They reacted against the strong colour range. Treponema pallidium, the spirillum causing syphilis, was discovered in 1905 by the Germans Schaudinn and Hoffmann. Recently a new infection has stricken the world and challenges our attitudes, values, feelings, prejudices and myths. This time, AIDS has once again prompted artists to illustrate illness and death. Keith Haring is one of the best known. He worked in New York and had an artistic education but became interested in graffiti art, which is common in New York where spray colours form dramatic images on busses and metro trains. Keith Haring was very productive and took part in many projects. He formed his own graffiti style and participated in many international art shows. Keith Haring was a homosexual. When he saw the AIDS victims around him, he took part in campaigns to make people understand the AIDS problem. Haring died of AIDS in 1990. His work contains many symbols and allusions to this illness. In a painting from 1988 Keith Haring wished to express his anger at the virus in the shape of the aggressive little figure emerging from the penis (Fig. 13). In another picture the symbol-
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FEATURES

Robert Mapplethorpe, a now very well known photographer, lived and worked in New York. During the late sixties and until the middle eighties his work included photographs of the sexual subcultures in Manhattan. Many of his pictures are strongly erotic, but he also photographed other objects such as his famous photos of flowers. His provocative photos caused much discussion in the USA, where the pictures were censored and the Cincinnati Contemporary Arts Center showing them was forced to close. Mapplethorpe was a homosexual and died from AIDS in 1989. One of his last photos is a self-portrait from 1988 (Fig. 15). His face has the mark of death and lies almost in darkness. The light is focused on the stick with the skull that he holds in his hand. This is an impressive and strong picture. In August 1992 the journal Science had a cover made by the American artist Brent Watkinson (Fig. 16). He has painted a deserted city with skeletons in the windows and dead people and skeletons in the street. In the background, a town is burning. Watkinson has juxtaposed the painting with a part of “The Triumph of Death” by Breughel. The diptych reminds us that devastating disease has long been part of world history and can be a reality again. This issue of Science contains articles about microorganisms resistant to antibiotics, e.g. pneumococci resistant to penicillin. We need to be vigilant of new infections caused by new agents. The spread of Ebola virus in Zaire was a reminder. Changes in the characteristics of old and well-known micro-organisms should also be carefully observed.

Anna-Stina Malmborg
In Response to Recent Events: Update on Bacillus anthracis

The recent outbreak of human anthrax infections in the USA, apparently caused by the deliberate spread of spores, has made all microbiologists and infectious disease specialists rush to renew their knowledge of this intriguing and historical disease. Anthrax has caused disease in animals and humans for many centuries. The common name is derived from the Greek word ‘anthrakis’, or coal, so named from the black cutaneous lesions produced. The disease anthrax is caused by the sporulating bacterium Bacillus anthracis, found in the soil in many parts of the world. The spores from infected animal carcasses can contaminate the pasture for many decades and lead to further sporadic outbreaks. Naturally acquired anthrax in humans is generally due to contact with infected animals or their carcasses. Although fatal human disease may occur, B. anthracis is not highly virulent, and in spite of its previous prevalence in the environment and animals, human infections were not common and are now rare. Virulence is associated with encapsulated strains and death is caused by toxins which produce massive haemorrhaging and shock. The most common form of the disease is cutaneous, which is frequently self-limiting. To produce the far rarer and serious form of inhalation anthrax, a large number of spores, greater than 1000, and possibly 5–10,000, are necessary to establish an infection. The genome of B. anthracis has been sequenced recently and considerable advances have also been made in understanding the mode of action of the toxins. The plasmids coding for toxins (pX01) and the capsule-associated plasmids (pX02) have also been identified and sequenced.

HISTORY
It is believed that the fifth and sixth plagues of Egypt, described in the Old Testament, were probably caused by anthrax, and also the descriptions of the ‘black bane’, which caused an estimated 60,000 deaths in cattle in Europe in the 1600s, indicate that this was anthrax. Two giants of early microbiology, Robert Koch and Louis Pasteur both studied anthrax in the 1870s. Koch demonstrated that the disease could be produced by the transfer of infected material from one animal to another. Pasteur continued this work, confirming the ‘germ theory of disease’ by using membrane filtration to prove that it was the bacilli that transferred the disease. Koch also demonstrated the ability of the bacillus to produce heat-resistant spores, which had the ability to germinate and infect animals. He thus explained what had long been a mystery: why animals continued to become infected long after infected animals had died and been removed from the pasture. Pasteur demonstrated in 1881 in a famous public experiment that cows, goats and sheep could be ‘vaccinated’ by use of a live attenuated strain. Soon after, vaccination of farm animals became commonplace and has remained so. The current vaccine is a live vaccine made from an unencapsulated, avirulent but toxigenic strain.

THE ORGANISM
B. anthracis is a large (1 x 3 mm), Gram-positive, rod-shaped, nonmotile, sporulating bacillus. The spores are central and thermostable. Like many other members of the genus Bacillus, the spores are remarkably resistant and long-lived in the environment. The organism grows rapidly on normal laboratory media (nutrient or blood agar) not needing any special cultural techniques, but does not grow on MacConkey agar. There are a number of morphological distinguishing characteristics; white-grey, flat or slightly convex, irregular round colonies with a ground-glass appearance. A ‘Medusa head’ colony is characteristic of B. anthracis. Cultures are not or very weakly haemolytic, but not β-haemolytic. In smears from infections, long chains may be formed and a capsule is present. The capsule can be seen clearly using India Ink. The lack of motility distinguishes B. anthracis from many other Bacillus species. Modern molecular techniques can be used to confirm strains of B. anthracis. Multiplex PCR has been used in recent outbreaks and immunohistochemical staining can be valuable.

OCCURRENCE
The disease is naturally one of animals, particularly herbivores, which ingest spores on the grass and from the environment. Until the advent of an effective vaccine, the disease was relatively common in cattle, sheep, goats, horses and pigs, but is now far rarer. Infections in humans were most often associated with the handling of infected animal carcasses or hides. ‘Wool sorter’s disease’ and ‘Tanner’s disease’ was contracted by those handling infected fleeces or hides, often from inhaling spores released in the processing of the fleeces or hides. Anthrax is still endemic in some parts of the world, notably Africa, the Middle East, Asia and some parts of the US and Australia. Anthrax is now a rare disease, with only 16 cases reported in the UK between 1980 and 2000. All were cutaneous cases, mostly associated with people working with bone meal, animal carcasses or skins. A human case occurred in North Dakota, USA, in 2000, the first since 1992. This case was associated with an epizootic among livestock. The man had handled cows dying of anthrax, and although he had worn leather gloves, he subsequently developed a lesion on his face, characteristic of anthrax. The disease was mild and responded to ciprofloxacin therapy. For several months during 2000, there were cases of anthrax among livestock on 31 farms in the area, compared with only two during each of the preceding 40 years. Inhalation anthrax is extremely rare under normal conditions, the last death reported in the UK was in 1974 and that was the first since 1965. In the US, even though anthrax is endemic in several states, only 18 cases have been reported in the 20th Century, the last in 1976.

HUMAN DISEASE
The commonest form of the disease, occurring in up to 95% of cases, is cutaneous. It is seen most often on the face, hands, forearms and
neck since infection is generally from handling infected material. The organisms, usually spores, invade from a skin abrasion or cut. After germination of the spores, the vegetative bacilli multiply locally and a small, visible papule, appears. This develops into a characteristic black, painless eschar with surrounding oedema. In most cases cutaneous anthrax is self-limiting, the lesion resolving within 10 days. In some cases systemic anthrax may develop, but unless therapy is initiated very late, by which time extensive toxin production has occurred, the disease responds well to chemotherapy. In untreated cases the death rate can reach 20%, but is less than 1% when treated.

Inhalation anthrax is rarer, comprising only approximately 5% of cases. Once established, however, this is a far more serious disease with a high death rate. The organisms do not multiply in the lungs but are carried by alveolar macrophages to the mediastinal lymph nodes where the spores germinate and multiply. From this focus they are able to spread rapidly throughout the body. Initial symptoms are insidious and flu-like, generally mild and non-specific. In the second phase there is acute respiratory distress, sepsis and an acute haemorrhagic mediastinal widening. X-ray symptoms can be confused with those of tuberculosis. Blood culture may be positive at this stage, and if the disease has progressed to this stage, it is frequently fatal as toxin production has already advanced and therapy can thus be ineffective.

Gastro-intestinal anthrax is even rarer and is contracted by consuming large numbers of spores, which infect the intestinal tract or the oesophagus. Unless there is a suspicion of anthrax, the difficulties in distinguishing these forms from other possible diseases means that, like in the case of inhalation anthrax, treatment may often be ineffectual.

Meningitis is a rare complication of any form of anthrax, and is generally fatal since, by the time it is diagnosed, toxin production is well advanced.

**TOXIN PRODUCTION**

Three toxins are produced by *B. anthracis*, all thermolabile proteins; a protective antigen (PA, 83kDa), an oedema factor (OF, 89kDa) and a lethal factor (LF, 90kDa). The individual toxins have no adverse effects, they need to combine to produce the characteristic toxicity seen in the disease. They target the macrophages and have little effect on other cells.

The protective antigen binds to receptors on the mammalian (macrophage) cell-surface and is cleaved by a cell-surface protease. This produces a cell-bound C-terminal 63kDa protein (PA63). This cleaved portion, PA63, has high affinity binding sites for the other two toxins. The bound complex enters the cell by receptor mediated endocytosis. The OF toxin has calcium and calmodulin-dependent adenylate cyclase activity. The LF toxin is a protease which interferes with the protein kinase signal transduction pathway.

**Box 1**

**Antimicrobial Susceptibility of 11/22 isolates of *B. anthracis***

(as on 24th October 2001 – MMWR Vol 50; No 42, 909)

**MICs (mg/l) are reported for the following drugs:**

* **Susceptible** *
  - Doxycycline ≤ 0.03, Tetracycline 0.06
  - Ciprofloxacin
  - Amoxicillin ≤ 0.06, Penicillin G ≤ 0.06 – 0.12
  - Rifampicin ≤ 0.5
  - Clarithromycin 0.25
  - Clindamycin 0.5
  - Vancomycin 1-2
  - Chloramphenicol 4

  Imipenem (fewer isolates tested) ≤ 0.12

* **Intermediate** *
  - Erythromycin 1
  - Azithromycin 2
  - Ceftriaxone 16

* In the absence of susceptibility breakpoints for *B. anthracis*, breakpoints were used for *S. aureus.*

Preliminary studies report the presence of a Class B cephalosporinase (constitutive) and the possibility of an inducible penicillinase.

**Therapy of current inhalation cases:**

- Combination intravenous treatment with Ciprofloxacin and rifampicin
- plus clindamycin
- or plus vancomycin
- or plus penicillin

The assembled toxin has powerful proteolytic activity which causes the eventual death of the macrophage. The release of cytokines, including IL-1 and tumour necrosis factor, from the damaged macrophages is believed to cause the damage to the blood clotting system and to contribute to the septic shock and oedema.
recently, these were the drugs of choice. Wild-type strains often produce a constitutive cephalosporinase. Penicillin-resistance has been noted, albeit rarely, in wild-type strains and, in addition, strains with resistance to penicillin are believed to have been engineered during the ‘cold war’ era. For these reasons, the first choice is now generally a fluoroquinolone, ciprofloxacin, although other fluoroquinolones are probably also effective. Most authorities still recommend that therapy be switched to a penicillin (penicillin G, penicillin V, ampicillin, amoxycillin) if antibacterial-susceptibility is confirmed. Alternative drugs include doxycycline, minocycline, erythromycin, clindamycin, vancomycin and chloramphenicol. Co-trimoxazole is not active and 3rd generation cephalosporins are not recommended.

For localised or uncomplicated cutaneous anthrax these doses are normally given for 7 days. The strains have all proved susceptible to ciprofloxacin, penicillins, tetracyclines, clindamycin, imipenem and clarithromycin, but erythromycin and azithromycin were less active. Antimicrobial susceptibility of 11 of the 22 isolates (as of October 24th) from the recent American cases of anthrax have been reported from the Centers for Disease Control (CDC).

The strains have all proved susceptible to ciprofloxacin, penicillins, tetracyclines, clindamycin, imipenem and clarithromycin, but erythromycin and azithromycin were less active. Antimicrobial susceptibility of 11 of the 22 isolates (as of October 24th) from the recent American cases of anthrax have been reported from the Centers for Disease Control (CDC).

VACCINATION FOR HUMANS
An adsorbed culture filtrate vaccine became available for humans some four decades ago and is generally used for those likely to be at high risk of exposure, including veterinarians, and military personnel. Protection is not long lasting and repeat vaccination is advised. Local reactions may occur. Because of the rarity of the naturally-occurring forms of the disease, however, there is little information on the degree of protection afforded against inhalation anthrax. Supplies of this vaccine in the US are reputed to be scarce, with only one company producing it. This company has had problems and is awaiting clearance from the FDA to commence large scale production. A live, toxigenic unencapsulated avirulent vaccine is available for animals, but this is not regarded as sufficiently safe to give to hu-

**Box 2**

**Summary of the Current Situation in the US**

*From Morbidity and Mortality Weekly Reports (MMWR) up to November 9th*

<table>
<thead>
<tr>
<th>Total numbers of anthrax cases</th>
<th>(as of Nov. 9th)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation anthrax</td>
<td>Confirmed 10</td>
</tr>
<tr>
<td>Cutaneous anthrax</td>
<td>Confirmed 7</td>
</tr>
<tr>
<td>Cutaneous anthrax</td>
<td>Suspected 5</td>
</tr>
</tbody>
</table>

Numbers of deaths: 4 (all inhalation anthrax)

Potentially exposed persons who received initial prophylaxis: 32,000

Numbers who continued with prophylaxis (60 days): 5000

**Important clinical characteristics of inhalation anthrax:**
- total WBC normal or only slightly elevated (7.5-13.3x10^3/cumm)
- increased % of neutrophils or band forms
- abnormal radiographs in 10/10 – but 2/10 needed very careful examination to detect the mediastinal widening
- pleural effusions present in 7/10 including the 2 patients with only marginal mediastinal widening
- blood cultures positive in 7/10
- if already receiving antibacterial therapy, cultures may be negative
- in those with negative blood cultures, PCR, immunohistochemical staining or a four-fold rise in IgG can confirm anthrax

**Important features in distinguishing inhalation anthrax from influenza-like illnesses (ILI)**

<table>
<thead>
<tr>
<th>Anthrax</th>
<th>ILI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal chest radiograph</td>
<td>10/10</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>8/10</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>8/10</td>
</tr>
<tr>
<td>Sore throat</td>
<td>2/10</td>
</tr>
<tr>
<td>Nasal congestion &amp; rhinorrhea</td>
<td>1/10</td>
</tr>
</tbody>
</table>

* pneumonia more common in the elderly
minds, although a live vaccine is apparently in use in Russia. Several groups are working on the development of new vaccines, but most are still at the experimental stage.

**ANTHRAX AS A BIOWEAPON**

As has been illustrated so clearly in the US recently, anthrax can be used as a weapon of terror. It is one of the favoured species for ‘germ warfare’ or bioterrorism, but is not necessarily an ideal one. It is not highly pathogenic, requiring a large number of spores to produce infection by any route. It is not transmitted from person-to-person other than in exceptional circumstances. The spores need to be transmitted in a very fine aerosol to be highly effective. To do this, very fine milling and the use of anti-caking agents are required to prevent the spores clumping. Those known to have been exposed can be protected by immediate chemoprophylaxis.

Nevertheless, as has been illustrated so graphically in the US recently, it can be the cause of great ‘nuisance’ and fear. If spores have been spread over a large area, because they are so resistant and long lasting, disinfecting a contaminated area is not easy.

A numbers of countries have attempted to develop anthrax as a bioweapon during the 20th century. The Germans were believed to have deliberately infected large numbers of cattle, goats and sheep in the first World War and a major outbreak of anthrax in Iran, which killed 1 million sheep was widely rumoured to have been part of a weapons programme.

During the 2nd World War the Germans were believed to have developed anthrax as a weapon, and to invest-expert who defected to the US, Russia developed highly sophisticated ways of using anthrax as a weapon. The accidental release of finely aerosolised spores from an extractor unit in one of the bioweapons sites, Sverdlovsk, in 1987 resulted in the death of over 60 civilians in the vicinity.

**WHAT OF THE FUTURE?**

It is clear from the recent outbreaks in the US that even if the delivery of anthrax spores has not been optimised, such attempts can pose a serious threat. In the early stages of an attack, if anthrax is not suspected, and if sufficient spores have been inhaled, fatal inhalation anthrax can occur. If the suspicion of anthrax is high and cases or those potentially exposed are identified rapidly, the disease is normally highly susceptible to a wide range of antibiotics. It is encouraging to hear of the ten people in the US with confirmed inhalation anthrax, six have survived, two of whom have been discharged from hospital. Rapid identification of the disease proved to be a key factor in their survival. As inhalation anthrax has many symptoms in common with influenza-like illnesses, CDC have issued guidelines to aid in distinguishing between the conditions (See Box 2).

Resistance can be developed experimentally to most of the current agents of choice, and it remains to be seen whether widespread use of ciprofloxacin and doxycycline will create a selective pressure on the organism. Vaccination is not a viable option currently for large numbers of people and supplies are not plentiful. In addition, the strain employed in the bioterrorist attacks in the US is thought to be the Ames strain, used originally in the US and the UK for their ‘Germ warfare’ pro- grammes. Vaccination is not thought to give full protection against this strain. Better methods of protection from the lethal effects of the toxins are required and various recent approaches may hold out some promise.

A DNA-based vaccine has proved itself to be of value in experimental work in mice. Plasmids coding for the PA and LF toxins were used by Galloway et al. to immunise mice who were able to survive over five times the usual lethal dose of anthrax. (Infect Immun 2001; 69: 4509)

Work published recently by Mourez et al. describes the identification of a peptide that binds to PA63. Multiple copies of this peptide were produced which functioned in vitro to prevent the binding of OF and LF to PA63. This peptide has also protected rats from a high dose of anthrax toxin. (Nature Biotechnology 2001; 19: 958)

An alternative approach has been described by Watters et al. who have isolated a gene, Kif1C, which encodes a protein responsible for organising the movement of proteins within the macrophage. By modifying this gene they have been able to protect mice from the lethal effects of anthrax toxin. (Current Biology 2001; 11: 503)

New methods of identifying strains can help in tracing the source of infection. A new technique (multilocus variable number tandem repeat analysis) can produce a genetic fingerprint of strains. Other approaches include the development of a mass spectrometer which can distinguish between anthrax and related species rapidly.

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Bacillus anthracis. Gram stain. CREDIT: CDC/Dr. William A. Clark

Pamela Hunter
Medical Writer
News in Brief

Prions and Transmissible Spongiform Encephalopathies

BSE IN JAPAN
The first known case of BSE in Japan was confirmed in a 5-year-old cow slaughtered in August. The tissues were sent to the UK for confirmation. Animal feed is thought to be a possible source of the infection and the Ministry of Agriculture is reported to be considering a ban on imports of feed containing meat and bone meal. There is already a ban on feeding bone meal to cattle, but there are claims that this has been violated. Beef sales have plummeted in Japan and many schools have stopped serving beef. The Ministry of Health has announced an expanded programme of testing in cattle, modelled on the system used by the EU. The cow was born in Japan, not imported, and thus it is likely that more cases may appear. This is the first confirmed case from Asia.

Reported by News Edge and New Scientist

BSE CONTINUES TO SPREAD IN EUROPE
The inexcusable spread of BSE continues, with the first case from Greece confirmed in July, two from the Czech Republic and one from Slovakia. Cases continue to occur in other European countries. The total numbers of cases confirmed since 1987 in countries other than the British Isles are now 767 in Ireland, 605 in Portugal, 447 in France, 395 in Switzerland, 126 in Germany, 70 in Spain, 54 in Belgium, 37 in Italy, 25 in The Netherlands and 6 in Denmark.

A suspected case in Sweden, which has had no cases substantiated yet, was not confirmed. The system of testing and control in Sweden has been criticised heavily by the EU for being ‘sloppy’, for not implement-
well-established. The author bases this claim predominantly on the fact that the numbers of cases are not growing at a rate one would expect from a foodborne source. He suggests that the so-called vCJD is a previously rare but misdiagnosed disease. The reason it is now recognised is because of heightened awareness.

GA Venter, BMJ 2001; 323:858

GERMAN GOVERNMENT INCREASES SPENDING ON TSE RESEARCH

The German government has announced that they are increasing the funding for research into TSEs by approximately tenfold. DEM 27 million will be made available for work to develop a test to detect prions in live animals and humans and work on therapy for prion diseases. Some of the work in cattle will be based at the Federal Research Centre for Virus Diseases of Animals on the island of Riems in the Baltic Sea.

Reported by Nature "News in Brief"

CAN BSE INFECTION SHEEP?

Since sheep can suffer from the transmissible spongiform encephalopathy (TSE) scrapie, which is a similar disease to BSE and is believed by many to have been the original source of the bovine disease, the obvious question is can BSE jump species and infect sheep? The UK government commissioned a study designed to answer this question some years ago. Just as this study was concluding, a "routine check" to ensure that there had been no contamination with bovine material revealed that there was some doubt that the material studied was in fact sheep brain and could be entirely bovine. It is not clear how the samples were misidentified or even by whom, but this matter has caused great embarrassment to all concerned.

www.defra.gov.uk

SCRAPIE

The sheep disease scrapie has been employed by an American group in investigating how prion diseases can adapt to hosts. They inoculated scrapie (from hamsters) into mice and found that, although there was no apparent disease and prion proteins could not be detected in the mice with current techniques, they were nevertheless harbouring the prions. Brain extracts from the healthy mice were able to produce scrapie when inoculated into hamsters. Also, when these mouse brain extracts were passaged in mice, disease symptoms appeared.


TSEs IN AMERICA

As noted before, although no cases of BSE have been identified in the US, a disease in wild deer and elk called chronic wasting disease with similarities to a TSE is widespread. It was reported previously that the US Department of Agriculture (USDA) had instituted a programme to cull infected animals. They have authorised $2.6 million to implement a surveillance programme on chronic wasting disease.

Reported by Environmental News Network

CONFIRMING PRIONS TO BE TESTED FOR ACTIVITY AGAINST PRIONS

A highly sensitive immunoblot technique has been developed which, it is claimed, will detect the abnormal prion protein PrPsc in tissues from those suspected of having vCJD. The work has been reported in the Lancet by a group from Imperial College, London. PrPsc could be detected in tonsils, spleen and lymph nodes in concentrations as low as 0.1% of those in the brain.

Wadsworth et al. Lancet 2001; 358: 171

INFECTIVITY OF EXTRAEPITHELIAL ABNORMAL PRION PROTEINS

In the same issue of Lancet, workers from Edinburgh, UK, tested the infectivity of abnormal prions found in extraneural tissues (spleen, lymph nodes, tonsils) of patients with vCJD. The samples were injected intracerebrally into mice and were able to produce disease but with a longer incubation period than is found with brain samples, indicating a lower degree of infectivity. Samples ofuffy coat and plasma were not shown to be infective.

M E Bruce et al. Lancet 2001; 358: 208

CHLORPROMAMINE AND QUINACRINE TO BE TESTED FOR ACTIVITY AGAINST PRIONS

Chlorpromazine, used to treat psychosis, and quinacrine, used to treat malaria and giardiasis, have been shown to be active in cell cultures against the abnormal prion protein PrPsc. Quinacrine was the more potent, and synthetic 9-substituted, acridine-based analogues have been prepared. Clinical trials with the parent compounds are planned to see if this efficacy is translated into clinical activity in humans with vCJD. It is intended for patients with late-stage disease to be recruited into a trial. This work was carried out in the laboratories of Stanley Prusiner.

C Korih et al. Proc Natl Acad Sci USA 2001; 98: 9836

Infectious Diseases and Outbreaks

CAN A HEPATITIS VIRUS COMBAT HIV?

Hepatitis G virus (HGV) was only discovered a few years ago (also called GB virus C). It appears to be harmless and to be common. Two studies, one from Germany and one from the US, reported in the New England Journal of Medicine have found that HIV patients co-infected with HGV had a greater survival rate than those who were not co-infected. A marked reduction in the replication of
HIV was seen in cell cultures infected with HGV. Diekama et al. and Tillman et al. New Engl J Med 2001; 345: 707 and 715.

**GOOD EFFECT OF INTERFERON ALpha-2b ON HEPATITIS C INFECTION**

Hepatitis C virus (HCV) often produces a chronic infection which is difficult to treat. A study of the beneficial effects of interferon alpha 2b carried out in Germany has given such good results that the New England Journal of Medicine has released the paper on its website prior to publication. Treatment was in the acute phase and in 42/43 patients treated, at follow-up, levels of HCV RNA were undetectable in serum. Only one patient were still free from infection which is difficult to cure. No evidence of resistance was observed.

**A NATURAL ANTIBIOTIC IS FOUND IN HUMAN SWEAT**

Dermcidin, a peptide secreted by human sweat glands, has been found to have broad spectrum antimicrobial activity. A group from Tübingen, Germany, discovered the antibiotic properties of dermicidin when looking for proteins involved in skin cancer. Dermcidin has activity against S. aureus, E. coli and C. albicans. The mode of action is not yet known. An unusual feature is that, unlike most other antimicrobial peptides, dermicidin is negatively charged, thus a general membrane effect is less likely.


**INHALED TOBRAMYCIN IN TREATMENT FOR CYSTIC FIBROSIS PATIENTS**

The airways of cystic fibrosis patients are frequently colonised with Pseudomonas aeruginosa, which can be difficult to eradicate and are usually treated with systemic antibiotics. The aminoglycoside tobramycin has been used as an inhalation in 15 cystic fibrotic children colonised with P. aeruginosa. The study was carried out in Essen (Germany). Treatment was twice daily for 1 year and in 14/15 of the children, the organism was eradicated. Two years after the end of treatment nine children were still free from infection. No evidence of resistance to tobramycin was observed.

F Ratjen et al. Lancet 2001; 358: 983

**RESISTANCE TO ANTIBIOTICS**

Three papers published recently in the New England Journal of Medicine were concerned with the transmission of antibiotic-resistant bacteria (Enterococcus faecium and Salmonella) found in food to humans. Streptogramin-resistant E. faecium were isolated from a high proportion of chicken from retail outlets in an American study (McDonald et al) but only from a small number of outpatients sampled. In a study in Denmark (Sørensen et al) volunteers were fed glycopenic- or streptogramin-resistant E. faecium from chicken or pork. The organisms survived passage through the stomach and were able to multiply in the intestine being detected in stools for up to 4 weeks.

**NEW EUROPEAN GUIDELINES FOR LEGIONELLA INFECTION**

A group in Germany has identified a key virulence factor, ‘macrophage infectivity potentiator protein’ (MiP) involved in preventing white blood cells from ingesting Legionella. The authors report the crystalline structure of this protein. A Riboldi-Tunnicliffe et al. Nature 2001; 413: 779

New European guidelines are being drawn up that will permit the names of hotels implicated in outbreaks of Legionnaire’s disease to be published on the Web. The guidelines have been submitted to the EC Communicable Disease Network Committee. The hotels named would be those from whom no information is available on control measures and investigations undertaken. The website is www.ewgli.com. Report by Reuters.

**NEW GENOME OF PLAGUE BACTERIUM SEQUENCED**

The genome of Yersinia pestis, the causative organism of bubonic plague, responsible for the infamous Black Death, has been sequenced by a group at the Sanger Centre, Cambridge, UK. The authors report that the genome is unusually fluid, with the capacity to pick up genes from other bacteria. The evidence suggests that originally Y. pestis lived in the human gut, later acquiring the ability to live in fleas (currently a vector for the disease). The genome contains 150 pseudogenes.

J Parkhill et al Nature 2001; 413: 523
to 14 days. In another American study (White et al.) 20% of ground meat samples (41/200) purchased at supermarkets were found to contain 13 serotypes of Salmonella species, 84% of which were resistant to at least one antibiotic. Ceftriaxone-resistance was found in 16% of isolates, and several isolates had multidrug resistance.

M O Donal et al., Sorensen et al., White et al. New Engl J Med 2001; 345: 1155, 1161, 1147

**NEW TARGET FOR CELL-WALL ANTIBACTERIALS?**

A group from the University of Lisbon, Portugal, and the Rockefeller University, New York, have reported a revised theory on the model of resistance to β-lactam antibiotics in methicillin-resistant staphylococci. Their work indicates that co-operative functioning of the transglycosylase domain of PB2 and the transpeptidase domain of PB2a is required for cell wall synthesis to take place in the presence of a β-lactam. The suggestion is made that the transglycosylation step would provide a good target for new compounds and that high throughput screens are now available to test for this activity.


**TARGETING METALLO-β-LACTAMASES**

The metallo-β-lactamase IMP-1 confers resistance to carbapenems. The structural basis of inhibition of this enzyme, with regard to stereoechemistry and the effect of substituents, has been investigated by workers from Merck in the US. The crystalline structure of the enzymes bound to an inhibitor has been elucidated. Toney et al. J Biol Chem 2001; 276: 31913

**RESISTANCE TO HIV DRUGS**

Resistance develops to HIV drugs with prolonged therapy in all three of the major classes of anti-retroviral drugs. A study from the UK has shown, however, that many HIV drug-resistant mutants are less fit than the wild type virus. If therapy was discontinued in patients carrying certain strains of resistant mutant HIV, the wild-type reappeared.


**Pharmaceutical Companies and Compounds**

**NEW APPROVALS**

TAP Pharmaceutical Products Inc. announced that the FDA has approved the cephalosporin Spectracef™ (ceftidoran pivoxil). Indications include pharyngitis/tonsillitis and uncomplicated skin and skin structure infections. Recommended dosage is 200mg or 400 mg twice daily for 10 days. Roche has received approval in the Netherlands for Valcyte™ (valganciclovir) to be used for AIDS-related cytomegalovirus (CMV) retinitis. Ganciclovir (Cymevene™) is currently available for CMV, but is an intravenous drug, whereas valganciclovir is oral. This is the first approval in the EU for Valcyte™. The EU have recommended marketing approval of Gilead’s anti-retroviral agent Viread™ (tenofovir disoproxil fumarate) in all 15 member states. Viread™ is a nucleoside reverse transcriptase inhibitor and available in a once-daily tablet for HIV patients who have failed previous therapy. The application was granted an accelerated review.

An NDA has been submitted to the FDA by ViroPharma Inc. for their new anti-viral agent Picovir™ (Plicanaril) for the treatment of the common cold. This is the first agent with claimed activity against picornaviruses. The drug is being progressed in the US jointly with Aventis. The ketolide Ketek™ (telithromycin) has been launched in Germany by Aventis for the treatment of community-acquired upper and lower respiratory tract infections in patients 12 years and older. The azole antifungal voriconazole (Viend™ Pfizer) has been approved by the FDA for the treatment of acute invasive aspergillosis.

**LINEZOLID AND REVERSIBLE MYELO SUPPRESSION**

There have been reports of myelosuppression associated with the oxazolidinone linezolid (marketed by Pharmacia), and a series of letters in the Journal of the American Medical Association have discussed this topic. Some authors have claimed a possible link between the effect on the bone marrow seen with linezolid and that seen with chloramphenicol, but this has been refuted by Pharmacia.

JAMA 2001; 286: 1973

**PFIZER SUED OVER TROVAFLOXACIN TRIALS IN NIGERIA**

Pfizer have been sued by a group of Nigerian families who claim that the Company violated international law and medical ethics when including children in trials of the use of trovafloxacin for treating meningitis. The claim is that Pfizer did not obtain informed consent or explain to the

**UNDESIRED ADJUVANT**

An extended phase III study with the most effective formulation is planned for the 1st Q 2002.

**GLAXO SMITHKLINE AND XENOVA TERMINATE HERPES VACCINE DEAL**

The failure of Xenova’s genital herpes vaccine (TA-HSV) in clinical trials has led to Glaxo SmithKline terminating its agreement with Xenova to develop the vaccine. Xenova will continue work on a prophylactic vaccine for genital and orolabial herpes.

Reported by Pharmafile

**TAISHO AND TANABA ANNOUNCE MERGER**

Taisho Pharmaceutical and Tanabe Pharma Group have announced that they are to merge. This will create the third largest pharmaceutical company in Japan.

**GLAXO SMITHKLINE GRANTS LICENCE TO GENERIC COMPANY IN SOUTH AFRICA**

The South African generics company Aspen Pharmacare have been granted a licence from GSK enabling them to produce cheaper versions of anti-retroviral drugs to combat the AIDS epidemic. The drugs are Epivir™ (lamivudine or 3TC), Retrovir™ (zidovudine or AZT) and Combivir™ (a combination of lamivudine and zidovudine).

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children or their parents that the treatment was experimental during an outbreak of meningitis in 1996. Médecins Sans Frontières (MSF) were treating children with chloramphenicol and are very critical of Pfizer’s behaviour. It is claimed that Pfizer treated 100 children with trovafloxacin and used ceftriaxone at a lower dose in a comparator group of 100 children.


**INTERMUNE LICENCE ELI LILLY ORITAVANCIN FROM INTERMUNE LICENCE ORITAVANCIN FROM ELI LILLY**

The biotechnology company InterMune has acquired the worldwide rights to develop and market the semi-synthetic glycopeptide oritavancin from Eli Lilly. Oritavancin is currently in Phase III development for use in skin and skin structure infections and in Phase II for bacteremia caused by Gram-positive organisms.

**ELI LILLY LICENCE RESQUMOD FROM 3M**

Eli Lilly has acquired the worldwide rights to develop and market the immune response modifier resquimod from 3M. The drug is currently in Phase II and Phase III trials for the treatment of recurrent genital herpes.

**European matters**

**THE EU COMMISSION CONSIDERS REFORM OF DRUG ADVERTISING LEGISLATION**

The EU Commission is considering proposals to reform the legislation of pharmaceutical drugs advertising. The stated aim is to provide consumers with better information on drugs for certain disease areas, but it is seen by various medical professionals as encouraging direct marketing to patients.

N Glass. Lancet 2001; 358: 306

**INFECTIOUS DISEASE SURVEILLANCE IN THE EU**

The efficiency of countries responding to outbreaks of communicable diseases is discussed in a paper and an editorial in the British Medical Journal. The conclusions are that the initiative set up by the EU in 1999 has proved itself to be of value, but certain weaknesses were highlighted. National surveillance should be improved and the authors suggest that the EU develops the existing surveillance networks.

L MacLehose et al. and LR Petersen & M Catchpole. BM J 2001; 323: 861 and 818

**ANTIBiotic USE CUT IN BELGIUM BY 12%**

Overuse of antibiotics is believed to play an important role in the increase in resistance to antibacterial agents and thus many authorities are keen to reduce consumption. In Belgium in the winter of 2000-2001 the public health authorities launched a campaign to do just this and it resulted in a reduction of 12% in antibiotic sales. The effect has now diminished and a new campaign is planned for this winter.

R Watson. BM J 2001; 323:710

Pamela Hunter
Medical Writer

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**Forthcoming events**

**ESC MID events:**

<table>
<thead>
<tr>
<th>Event Details</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>22–23 April 2002 18th ESC MID Postgraduate Education Course: Diagnostics, Characterisation and Epidemiology of Beta-Lactamases, Osa San Giulio, Italy</td>
<td>Guiseppe Cornaglia, MD, Dept. of Pathology (Microbiology Section); University of Verona, Strada Le Grazie 8; I- 37134 Verona, Italy Phone: +39-045-802 7196, E-mail: <a href="mailto:guiseppe.comaglia@univr.it">guiseppe.comaglia@univr.it</a></td>
</tr>
<tr>
<td>24–27 April 2002 12th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Milan, Italy</td>
<td>Dr. Vicente Javier Benedi, Dept. of Microbiology, Universidad de las Islas Baleares, Cametra de Valldemossa, Km 7,5, 07071 Palma de Mallorca, Spain. Phone: +34-971-17335 E-mail: <a href="mailto:vbenedi@ab.es">vbenedi@ab.es</a></td>
</tr>
<tr>
<td>16 – 22 June 2002 19th ESC MID Postgraduate Education Course: Mechanisms of Antimicrobial Resistance – A Practical Approach, Palma de Mallorca, Spain</td>
<td>Julie Griffith E-mail: <a href="mailto:jq@internar.be">jq@internar.be</a></td>
</tr>
<tr>
<td>10–13 May 2003 13th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Glasgow, UK</td>
<td>Julie Griffith E-mail: <a href="mailto:jq@internar.be">jq@internar.be</a></td>
</tr>
<tr>
<td>1–4 May 2004 14th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Prague, Czech Republic</td>
<td>Julie Griffith E-mail: <a href="mailto:jq@internar.be">jq@internar.be</a></td>
</tr>
<tr>
<td>2–5 April 2005 15th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Copenhagen, Denmark</td>
<td>Julie Griffith E-mail: <a href="mailto:jq@internar.be">jq@internar.be</a></td>
</tr>
</tbody>
</table>

**In co-operation with ESC MID**

<table>
<thead>
<tr>
<th>Event Details</th>
<th>Contact</th>
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</thead>
<tbody>
<tr>
<td>15 December 2001 Global White Paper on Bacterial Resistance in Community-Acquired Respiratory Tract Infections - IFAR Symposium at the 41st ICAAC 2001 (see below), Chicago, IL, USA</td>
<td>Julie Griffith E-mail: <a href="mailto:jq@internar.be">jq@internar.be</a></td>
</tr>
<tr>
<td>17–19 March 2002 Medical Biofilms 2002, International Conference, Tokyo, Japan</td>
<td>Julie Griffith E-mail: <a href="mailto:jq@internar.be">jq@internar.be</a></td>
</tr>
</tbody>
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**CALENDAR**

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**EXCERPTS**

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**ESCMID NEWS**

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**ESCMID**

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**VINE**

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**EXCERPTS**

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**EXCERPTS**
Other events:

12–14 December 2001
5th International Symposium on Febrile Neutropenia, Brussels, Belgium
Contact: Prof. J. Klastersky
Phone: +32-2-541 3201
Internet: www.febrileneutropia.org

14–16 December 2001
1st International Meeting on Penems, Carbapenems and Related Compounds, Venice, Italy
Contact: Progetti di Congress Studio Srl
Phone: +39-02-319 6951
E-mail: info@congress-studio.it

15–19 December 2001
41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, USA
Contact: ASM Conferences
Phone: +1-202-942 9248
Internet: www.asmusa.org

22–24 April 2002
HPC, Bacteria in Drinking Water - Public Health Implications?, Geneva, Switzerland
Contact: Bob Tanner, NSF International
Phone: +32-2-771 3654
Internet: www.nsf.org/conference/hpc

23–26 January 2002
European Conference on Viral Disease (ConVir 2002), Munich, Germany
Contact: J.R. Bogner
Phone: +49-89-5160 3598
Internet: www.convir2002.de

4–7 May 2002
4th European Congress of Chemotherapy and Infection (ECC), Paris, France
Contact: Congrex Sweden
Phone: +46-8-459 6600
Internet: www.congress.com/ecc-4

10–12 May 2002
European Conference on Vaccine Development (ICL02), London, UK
Contact: HPC, Bacteria in Drinking Water - Public Health Implications?, Geneva, Switzerland
Contact: Bob Tanner, NSF International
Phone: +32-2-771 3654
Internet: www.nsf.org/conference/hpc

24–27 July 2002
6th International Meeting on Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases (MEEGID-VI), Paris, France
Contact: Alastair A. Lal
E-mail: aatl@cdc.gov
Internet: http://cepm.mp.lru.fr

27 July – 1 August 2002
The World of Microbes - Joint Meeting of the Divisions of the International Union of Microbiological Societies, Paris, France
Contact: ICA/JCD Conseil
Phone: +33 (0)1 4064 2000
Internet: www.iums-paris-2002.com

18–22 August 2002
9th International Conference on Lyme Borreliosis and other Emerging Ticks-Borne Diseases, New York City, NY, USA
Contact: Heather Drew, Imedex
Phone: +1-770-751-7332
Internet: www.imedex.com

8–12 September 2002
3rd European Congress on Tropical Medicine, Lisbon, Portugal
Contact: Steven Talbourn, K.T.I. GmbH
Phone: +49-30-24603-301
E-mail: tropical2002@ikt.de

15–19 September 2002
5th International Conference of the Hospital Infection Society (HIS), Edinburgh, UK
Contact: HIS 2002 c/o Concorde Services Ltd.
Phone: +44-141-331 0123
Internet: www.his2002.co.uk

28–30 September 2002
42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, CA, USA
Contact: ASM Conferences
Phone: +1-202-942 9248
Internet: www.asmusa.org

19–24 October 2002
4th International Conference on Therapies for Viral Hepatitis, Isla Verde, Carolina, Puerto Rico
Contact: ASM Conferences
Phone: +1-202-942 9248
Internet: www.asmusa.org

23–26 October 2002
4th International Meeting on the Therapy of Infections (IMT), Florence, Italy
Contact: 4th IMT Organising Committee
Phone: +39-035-427 9478
E-mail: info@congress-studio.it

27–30 January 2003
34th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, USA
Contact: ASM Conferences
Phone: +1-202-942 9248
Internet: www.asmusa.org

1–5 December 2002
10th Annual Scientific Meeting of SHEA, Arlington, VA, USA
Contact: SHEA Meetings Department
Phone: +1-856-423 7222
Internet: www.shea-online.org

1–10 June 2003
23rd Interscience Conference on Chemotherapy (ICC), Durban, South Africa
Contact: 23rd ICC Secretariat c/o Congrex Holland bv
Phone: +31-20-5040 200
Internet: www.congress.nl/icc2003

29 June – 3 July 2003
1st European Congress of Microbiology, Ljubljana, Slovenia
Contact: Federation of European Microbiological Societies (FEMS)
Internet: www.fems-microbiol.org

21–23 September 2003
3rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Toronto, ON, Canada
Contact: ASM Conferences
Phone: +1-202-942 9248
Internet: www.asmusa.org