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Sesión plenaria: Symposio sobre bioterrorismo, grandes amenazas epidémicas y bioseguridad: sesión II (agentes y funciones del CDC europeo)

Auditorium, Facultad de Farmacia
Martes 20 de Julio: 11.00-13.30

175.- The need for a European Centre for Infectious Diseases with large competences and coordination capacities

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The news of the creation of the European Commission project "European Centre for Disease Control" (ECDC) is causing a stir[1]. This is not deserved. The project is for sure a progression in comparison with the vague concept of a "virtual CDC" (connecting the existing centres by electronic communication)[2,3]. However, it remains a pale and tiny imitation of the reference structure for the whole world: the US CDC, based in Atlanta, and staffed with no less than 1,500 people working full time on transmissible diseases. By comparison, the ECDC will have a staff of only 50. This is a glaring disproportion. Even a national structure, the French Institut National de Veille Sanitaire, has a personnel of 250.

The project for the "European Centre for Infectious Diseases" (ECID)[4,5] involved a planned staff of 500, which matches better its US model. However, size is not the only problem with the ECDC. The successful recipe of the US CDC is its triple mission of advanced research, surveillance/control and professional training. This concept was retained for the ECID too, while the ECDC will limit itself to a tiny administration. A historical opportunity will be missed to bless the birth of the great Europe of 25 with an ambitious project on the scale of its means and of its needs. Apart from the key role that an ambitious European CDC could have in facing major epidemic and bioterrorism threats, and in boasting European biomedical science, this kind of highly symbolic enterprise is sorely needed to give the new Europe a dimension of peaceful historical epopee instead of this sad face of sordid economical bargaining.

It is unexpected that no public debate was held among the European scientific and medical community before launching this minimal project. Whatever be the competence and dedication of its staff members, the ECDC won't be enough to face major epidemic disasters, and Europe will be unable to counter the irresistible advance the USA are taking in this key field through efficient structures and massive investment. The only hope that is left to those who dream about other ambitions for our Europe is that the ECDC will be only a first step, a pilot project towards a euro-CDC worthy of the name, attractive for our young talents and vector of the scientific and medical prestige of our continent[6].

(1) Watson, R., 2004. Europe to have its own centre for disease control. *British Medical Journal* 3328, 426.

(2) The Editor. 1998. Not Another European Institution. *The Lancet* 352, October 17: 1237.

(3) MacLehose, L., McKee, M., Weinberg, J., 2002. Responding to the challenge of communicable disease in Europe. *Science* 295, 2047-2050.

(4) Tibayrenc, M., 1997. Microbes Sans Frontières and the European CDC. *Parasitology Today* 13 (12), 454.

(5) Tibayrenc, M., 1997. European Centres for disease control. *Nature*, 389, 2 October, 433.

(6) Tibayrenc, M., 2004. The European Commission pocket CDC: encore un effort!. The Lancet Infectious Diseases.

176.- The European Centre for Disease Prevention and Control

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In a European Union where millions of people cross external borders each day, tackling health threats requires a much closer co-operation between Member States, the European Commission, the World Health Organization and affected countries around the world. Moreover, the European Union has created a single space for more than 450 million people in which persons, goods, capital and services can circulate freely and the risks from spreading harmful agents would be greater if measures to stem their progress at source are not taken. The European Union citizens place a very high value on the protection of their health.

Since end 1998, the Commission has managed the Community Network for the Epidemiological Surveillance and Control of Communicable Diseases. This organizes the co-ordination of national surveillance systems and institutes/agencies on the basis of a common list of diseases under surveillance[1], common case definitions and common laboratory methods[2]. It also provides for close co-operation between the Member States of the European Union within the legal framework of European Parliament and Council Decision 2119/98/EC[3]. Moreover, the Community Network comprises also an Early Warning and Response System (EWRS)[4] which connects the competent authorities of all the EU Member States responsible for notifying formally outbreaks of disease in the common list and for communicating in advance and in good time information on counter-measures, or information on measures already taken if these had to be taken without delay.

However, there is a need for a substantial reinforcement of this system if the European Union is to be in a position to face up to the increasing demands of control of communicable diseases effectively. The epidemics of SARS in 2003 and avian influenza in 2004 have clearly demonstrated the havoc and panic that emerging diseases can wrought. Pandemic influenza remains a constant threat and new pathogens with longer incubation periods may still emerge out of the incessant encroachment of previously untouched habitats, intensive farming without proper hygiene and safety conditions, spreading cultural habits, trade -often illegal- in exotic pets (and used tyres) and fast transport which incapacitates traditional methods for containment.

This led the European Commission to propose the establishment of a European Centre for Disease Prevention and Control. The proposal aims at creating an agency able to provide a structured and systematic approach to the control of communicable diseases and other serious health threats which might affect European Union citizens. The ambition is to start with a body which would mobilize and significantly reinforce the synergies between the existing national centres for disease control and evolve, in time, to a centre of excellence to rival its illustrious US counterpart, the Centers for Disease Control. The proposal was agreed by the European Parliament and the EU Council of Ministers on 31 March 2004.

The main tasks of the European Centre for Diseases Prevention and Controil include:

Epidemiological surveillance and networking of laboratories: The Centre would develop epidemiological surveillance at European level. In this work, the Centre could either use its own staff, staff from established surveillance schemes, or, in some instances, it could subcontract tasks to national centres. The Centre could also identify and maintain networks of reference laboratories and enhance the quality assurance schemes of microbiological laboratories. It will collect, evaluate and disseminate scientific and technical data, maintain the databases for epidemiological surveillance, provide technical assistance and training and facilitate the exchange of information, sharing of expertise and the development and implementation of joint actions.

Early Warning and Response System: To be effective the EWRS requires 'around the clock' availability of specialists in communicable diseases. Whilst the responsibility for measures and their notification, as well as their co-ordination will remain with the Member States and the Commission, technical operation of the EWRS would be undertaken by the Centre and its networks. The Centre will also hook up with other rapid alert systems operated in the European Union.

Scientific opinions: Public health decisions have to be based on independent scientific evidence. Scientific issues arising in the area of communicable diseases vary widely, ranging from questions of clinical medicine and epidemiology through to standardization of laboratory procedures. The Centre would bring together scientific expertise in specific fields through its various EU-wide networks and via ad hoc scientific panels and would issue advice and scientific opinions following the request of the European Commission, the Member States or the European Parliament.

Technical Assistance and Communication: The Centre's rapid reaction capacity could cover more than the European Union itself, to similar structures in such areas as the EEA/EFTA, and candidate countries. When requested, it would send an EU-team to investigate an outbreak of an unknown human disease in a European country. The Centre should also have the ability to support, if necessary those Commission services that give humanitarian aid or other types of assistance in response to disease outbreaks in third countries.

Objective, reliable, and easily accessible information is essential for the general public and as well as for decision-makers in the Commission, Member States and international organizations. The Centre will communicate about its activities and results, and disseminate information tailored to meet the needs of its different audiences. Using various media and communications tools, the Centre will ensure that its information is easily accessible, reliable, and understandable.

Management: To assist the Centre's management, a Management Board will be established composed by one member designated by each Member State, two members from the European Parliament and three members representing the European Commission. A Director will be appointed by the Board for five years renewable once following an open competition from a list proposed by the Commission. Moreover, an Advisory Forum will be set up to support the Director in ensuring scientific excellence and independence of activities and opinions of the Centre. Its members will be designated one each by each Member State and three by the Commission control of communicable diseases.

The Centre will be based in Stockholm, Sweden. Its operation is foreseen for May-June 2005.

(1) Official Journal of the European Communities, L 86, 3.4.2002, p. 44.
(2) Official Journal of the European Communities, L 28, 3.2.2000, p. 50.
(3) Official Journal of the European Communities, L 268, 3.10.1998, p. 1.
(4) Official Journal of the European Communities, L 21, 26.1.2000, p. 32.
(5) Official Journal of the European Communities, L 184, 23.7.2003, p. 35.

177.- Targeting the anthrax toxin complex: development of new detection, prophylaxis, and treatment strategies

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Anthrax is category A hazardous infectious disease primarily affecting humans and livestock. Although there is a number of natural anthrax reservoirs throughout the world, and sporadic disease outbreaks occur from time to time, natural anthrax is efficiently controlled by vaccination and antibiotic therapy. Until recently, the threat of the anthrax epidemic for civilian population has been considered as negligible. However, use of weaponized powdered anthrax spores by terrorists has become a reality. Although the source of the weaponized anthrax used by the terrorists is still unknown, anthrax spores could be readily isolated from the natural pestholes making prevention of the pathogen acquisition by the malefactors virtually impossible. Anthrax spores are extremely resistant to inactivation by disinfectants and can be stored for tens of years without loss of infectivity. All these features make anthrax the most attractive candidate for bioterrorism and germ warfare. Development of efficient tools for prevention, diagnostics, and treatment of inhalational anthrax is therefore critically important.

Recent bioterrorist attack with aerosolized anthrax spores revealed limited capability of modern healthcare system to timely diagnose and treat inhalational anthrax. Current anthrax treatment and prophylaxis is nonspecific and relies upon use of tetracycline and fluoroquinolone antibiotics. However, with mounting of high toxin concentration in the bloodstream antibiotic therapy of anthrax fails. Thus, for successful antibiotic treatment, early diagnostics of inhalational anthrax is vitally important. At the same time, diagnostics of inhalational anthrax is hindered by the fact that early symptoms are nonspecific and are "flu-like". The only approaches currently available for rapid detection of anthrax are PCR-based and ELISA-based tests. However, these techniques do not determine biologically active anthrax components such as toxin. Thus, PCR and antibody-based detection could fail if genetically modified pathogen carrying no relevant targets is used. Furthermore, use of various live "mockups" carrying the targets for PCR or immunoassay tests could result in false-positives thus causing unnecessary alerts. Major pathological determinant of *Bacillus anthracis* is the tripartite toxin consisting of the receptor-binding component also known as protective antigen (PA), and two effectors, lethal factor (LF), and edema factor (EF). All three components are proteins secreted by the pathogen once it enters nutrient-rich environment and germinates from endospores. A reliable error-free anthrax detection system would be based on determination of the active anthrax toxin. The functional test for the lethal toxin component, the LF endopeptidase, is the most prospective for development of the new anthrax assay suitable for application in the clinic. The key assay component is the short peptide substrate cleaved by LF with high efficiency and specificity. Currently available LF peptide substrates are not suitable for development of the anthrax clinical test. They are cleaved by LF with low efficiency and contain stretches of basic amino acids making them good targets for cleavage by trypsin- or furin-like proteases potentially contaminating the clinical specimens. Use of "substrate phage display" approach permits identification of short peptide substrates efficiently cleaved by a given protease. Furthermore, selected by substrate phage display and bearing high complementarity to primary and secondary catalytic determinants of the protease could be used in development of new anti-anthrax therapeutics.

Vaccination against anthrax is probably the best way to protect humans from a bioterrorist attack. Currently available anthrax vaccines existing in Russia and abroad were developed decades ago. These vaccines have a number of significant shortcomings limiting their widespread use in civilian population. Although the live attenuated Russian vaccine, as well as aluminum-adsorbed Sterne vaccine employed in a number of countries are efficient against sporadic natural infection, these could fail against aerosolized formulation that is capable to infect one human subject with billions of spores. In addition, available vaccines could be unacceptable for use in e.g. children, elder, and in some other categories. Standardization of protection conferred by these vaccines is hindered. In particular, the PA level is not assayed in the vaccines, and the standard assay for neutralizing activity of antibodies produced after vaccination is lacking. There is a need to develop a new-generation anthrax vaccine. Such a vaccine must include only well-characterized components proven to induce anti-anthrax protective immunity. The only know toxin component whose protective effect is proven is the anthrax PA. It is therefore logical to use the PA as the principal component of the new vaccine. It is known that the antigenic structure of PA is complex. Mature PA has a molecular weight of 63 KDa and consists of four domains. The level of protective immunity induced after immunization with various PA domains varies significantly. The subunit vaccine containing the engineered PA epitopes inducing toxin neutralizing antibodies would be designed to achieve the maximal protective effect. At the same time, such a vaccine is amenable to simple standardization with respect to the induced neutralizing antibody titer. Although the value of mapping the neutralizing PA epitopes is evident, little data has been so far obtained. We prepared a panel of mouse anti-PA mAbs and studied the immunological properties of the panel members displaying highest affinity to PA. We found that one anti-PA mAb (1F2) possesses the unusual toxin-enhancing activity judging by significant increase in toxin-mediated killing of macrophage-like cell line in the presence of this mAb. A phenomenon of antibody-mediated enhancement of viral infection is known, but it has been described for a bacterial toxin for the first time. We also described new toxin-neutralizing mAbs, 6G8 and 6G9. Preliminary epitope mapping showed that the toxin-enhancing and toxin-netralizing mAbs are specific to different domains of the PA. Discovery of the toxin-enhancing antibody specific to the anthrax PA strongly indicates the need for development of new-generation engineered anthrax vaccine.

In the present communication, the principal elements of the integrated approach for combating anthrax are discussed.

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178.- Development and application of real-time PCR assays to detect fragments of the Clostridium botulinum types A, B and E neurotoxin genes for public health microbiology including deliberate release

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Clostridium botulinum is one of the potential agents of deliberate release and the current routine method for diagnosis, detection and identification relies on assays for neurotoxin (BoNT) activity using a mouse bioassay. The bioassay is labour intensive, slow, and expensive to perform. There are seven BoNTs (designated A, B, C, D, E, F and G), of which A,B,E and F have been associated with human infection. Real time PCR assays for detection of BoNT gene fragments specific to BoNTA, B and E were developed based on hydrolysis probe (TaqMan) chemistry. The PCR assays were initially developed using target DNA extracted from 23 pure cultures of *C. botulinum* and 21 *Clostridium* from 14 other species from the culture collections which were grown *in vitro* on agar and in broths. The assays were then applied to DNA; directly extracted from 50 clinical or food samples; from 39 enrichment cultures inoculated with naturally contaminated food or clinical material; and from wild type cultures growing on solid media of 58 *C. botulinum*, 2 *Clostridium sporogenes*, 10 *Listeria* and 10 *Bacillus*. The assays were rapid, sensitive, reproducible, easy to perform and specific: the same BoNTs were detected by the bioassay as by PCR in all except four of the samples. These assays have already proven useful for pubic health microbiological investigation of suspected cases of human botulism by substantially improving the diagnostic process. The assays will also be useful in the rapid investigation of deliberate release incidents where contamination of foods and the environment by *C. botulinum* is suspected.

179.- Psychological aspects of weapons of mass disruption (WMD)

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The importance of the psychological effects of chemical, biological, radiological/nuclear and high explosive (CBRNE) weapons is increasingly being recognized in the post-9/11 era. CBRNE agents are often referred to as "weapons of mass destruction" or "WMD". However, with the exception of nuclear weapons and high explosives, most of the WMD do not cause large-scale physical destruction. Perhaps a better term would be weapons of mass disruption, as these weapons can cause mass casualties along with extreme psychosocial effects. Terrorism involving weapons of mass disruption (WMD) may have powerful psychosocial consequences.

This presentation will review the research on traumatic incident stress following chemical, biological, radiological and nuclear (CBRN) accidents and intentional use. Some reactions are rare, such as mass panic, while others are more common, such as outbreaks of multiple unexplained symptoms (OMUS, often referred to as mass hysteria or mass psychogenic illness). Traumatic incident stress may produce large numbers of casualties that could rapidly overwhelm medical capacity. In many cases, symptoms from traumatic stress (flu-like symptoms, such as fatigue, malaise, headache, arthralgia, myalgia, dizziness, dyspnea, and weakness) may be similar to prodromal symptoms seen following exposure to CBRN weapons. The term "worried well" is often used to refer to stress reactions. However, the term is not only misleading, but also pejorative and should not be used. Casualties seen in a WMD event will certainly be worried, with good reasons to be. However, if they are symptomatic, they are not well and should not be dismissed with the label "worried well". These non-specific symptoms can lead to difficulties in differential diagnosis. Hyperventilation syndrome may be a physiological explanation for some of the non-specific symptoms. Remember that psychological reactions may exacerbate symptoms and distress in those injured in a WMD event. Examples from historical WMD accidents and attacks show that they can result in large numbers of psychological casualties. There will be a complex of effects which will include acute psychological casualties, long-term psychological casualties, and large-scale psychosocial consequences such as economic disruption, evacuation and/or relocation of portions of the population. The psychological effects will not be unique, but will be similar to those seen after natural and technological disasters, and attacks with conventional weapons. There likely also be an increase in ill-defined, chronic-fatigue-like syndromes with multiple unexplained physical symptoms.

Many of these effects can be prevented or mitigated by proper planning and practice prior to a CBRN event. Health risk communication both pre- and post-event will be critical for prevention and mitigation of psychological effects.

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