BIOLOGICAL RISK AND PATHOGEN CONTROL:
LEONS FROM THE STUDY OF EMERGING DISEASES

Prepared by France

1. Biological risks are, broadly speaking, linked to accidental, natural or criminal release of agents that are pathogenic for humans, other animal species or plants. These pathogens can in theory be either natural or genetically modified. Their dissemination can impact all parts of society, with effects ranging from panic with unpredictable economic consequences to outbreaks of full-blown epidemics or pandemics.

2. Prevention of such risks should address a number of factors:
   a. Ability to detect a new infectious risk;
   b. Existence of systems able to rapidly address the scientific issues raised by the pathogen;
   c. Ability of the health care system to efficiently and effectively manage infected patients when the agent is a human pathogen;
   d. Responsiveness of the community as a whole and in particular its ability to manage and prepare for crises.

3. One way to comprehensively and constructively approach biological risk issues is to study emerging or re-emerging diseases and the structural changes that these have brought about. The end of the twentieth century offers a wealth of such cases; over a 30 year period the world witnessed the emergence of HIV, Hepatitis C virus, Ebola virus and the Bovine Spongiform Encephalopathy (BSE) agent that causes variant Creutzfeldt-Jakob Disease (vCJD) in humans. To address these new public health challenges, health care systems have had to adapt, or try to adapt, to the specific constraints of the new diseases, especially the HIV pandemic. The success and pace of the adjustment have depended, for the most part, on the budgets governments were able to make available.

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4. Risk management also changed quite considerably; the change, clear-cut in the developed countries, was often driven and sometimes initiated by awareness on the part of the public, or that part of the public that was particularly affected. Over a 20 year period, microbiological safety of medicinal products, surgical instrument sterilization procedures and the doctor/patient relationship underwent profound change as a result of the health crises caused by the emergence of HIV infection, cases of CJD linked to extractive growth hormone, the appearance of Hepatitis C and infection of humans with the BSE agent.

5. As a result of these upheavals, medical science lost its aura of omnipotence, the doctor/patient relationship became more of a two-way street with the physician and the patient sharing scientific certainties and doubts, and a health system was set up at national and community level to anticipate future biological risks.

**HIV infection: spread and public health implications**

6. In the early 1980s M. Gottlieb observed the appearance in young homosexual males of severe immune deficiency resulting in serious infections by opportunistic pathogens, tumors and fatal encephalopathies. The new disease was observed a short time later in heroin addicts and Haitians and was soon suspected of being linked to a transmissible agent. A group of French clinicians, hospital virologists and researchers discovered the etiological agent, a lentivirus belonging to the retrovirus family. This class of viruses is able to insert its genome into the host genome even when the infected cell is quiescent or in the G1 cell cycle phase.

7. This property makes it difficult to devise an effective therapy to eradicate the virus and to define appropriate vaccine strategies. In addition, the virus infects key immune response cells - CD4+ lymphocytes and macrophage-line cells - and thus disrupts the body's overall infection-fighting capability. This Trojan horse strategy contributes to establishing chronic HIV infection and explains the (at least partial) ineffectiveness of the specific immune response. To enter its target cells, the virus uses molecules that are key to the dialogue between the various cell populations involved in immune response, the CD4 molecule and the chemokine receptors. Finally, it sometimes diverts the host's immune response for its own benefit: for example, its opsonization by complement enables it to use the complement receptors located on the surface of certain types of cells to infect them.

8. The appearance of a virus of this family in human medecine came as a shock and had major implications. The first difficulty faced by the medical community was to realize that in the medium term the HIV infection was going to spread inexorably. The analogy of Hepatitis B Virus (HBV) infection, in which only a small number of infected subjects develop serious forms of the disease, was difficult to overlook. Hence, with the exception of infectious disease specialists and retrivirologists, the medical profession failed to appreciate the scale of the developing epidemic in the 1980s.

9. Epidemiologically, at least at the beginning, HIV infection affected only a few groups of people (intravenous drug abusers, Haitians, homosexuals), and the "selective" nature of the disease gave rise to or reinforced community-focused attitudes. Scepticism about the scale of the coming epidemic, the absence of a precedent (no
human disease was linked to a lentivirus) and the presence of strong leaders in the support groups soon generated a parallel patient-focused flow of information alongside the conventional medical community-to-public information flow, with the result that, at times, patients and physicians acquired knowledge concerning the disease simultaneously.

10. This brought about a profound change in the doctor/patient relationship, with doctors sometimes perceiving patients as overly demanding. For the most part however the medical community accommodated patients' requests and learned to share diagnostic doubt and to discuss therapeutic strategies and prevention methods. The change no doubt also reflects the chronic nature of the infection, the long periods of treatment of those infected and their youth and social status at the time of diagnosis. The demand by patients to be allowed to share medical knowledge and decision-making has also had an impact on the organization and design of therapeutic testing when such testing was possible - patients were involved in the development of new drugs and some demanded access to treatments before the latter had received full regulatory approval.

11. Alongside the changes taking place in the doctor/patient relationship, another profound change was taking place in procedures relating to the safety of medicinal products of biological origin and of transfusions. Cases of infection in hemophiliacs treated with medicines derived from blood plasma and in a number of persons who had received transfusions prompted a radical overhaul of the criteria applying to the use of medicinal products of biological origin.

12. The public health care authorities acted swiftly to spell out standard procedures for a-priori viral safety analysis of medicinal products of biological origin (drugs and medical devices); the procedures provided a better definition of potential risks and a more accurate appreciation of the risk/benefit ratio. Conventionally the safety of a medicine of biological origin depends on three factors:

   a. donor selection;
   b. ability of the manufacturing process to inactivate and/or eliminate the virus;
   c. microbiological testing carried out during manufacture and on the final product.

13. These three factors act together to foster safety and should never be considered separately.

14. This "drug safety philosophy" is a direct consequence of the infection of hemophiliacs with HIV. The approach has been gradually formalized and the first European guidelines were issued in the late 1980s and early 1990s. Nationally, the health authorities set up an expert group of virologists charged with analyzing the risk/benefit ratio of drugs approved either for marketing or for clinical testing. This group of independent experts became the standing "Viral Safety Group" under the institutional reforms that have taken place starting in 1990. In practice this has meant:

   a) better selection of donors (more extensive questioning, effective screening, optimization of detection methods as technology progresses, as in the introduction of methods based on molecular biology);
b) a precise review of manufacturing processes with a focus on safety. To this end, at the end of the 1980s, "viral validations" were introduced to provide maximum safety in drug manufacturing procedures. This approach, based on model viruses representative of the intrinsic raw material risk, defines the ability of manufacturing processes to inactivate and/or eliminate known viruses. In practical terms, the preparation process for a given biological derivative is miniaturized and then the initial material is loaded with a known quantity of infectious agent and the ability of one or several phases of the manufacturing process to purify and eliminate and/or inactivate the agent is assessed. It is then possible to quantify the clearance factor of a manufacturing process for a given virus. The choice of viruses to be studied is critical; pathogenic viruses potentially present in the initial material should be used whenever a viral stock of high infectious titre can be produced \textit{in vitro} and methods exist to measure viral replication. For example it will be virtually mandatory to use HIV-1 in validation studies of purification processes used for plasma-derived products. However, it is not always possible to use the pathogenic viruses most involved in accidental transmission, for lack of an appropriate culture system. This is true of the Human Hepatitis B and C (HBV and HCV) viruses which it has so far been impossible to culture \textit{in vitro}. In these cases, it is necessary to use “model” viruses of the same family or have similar physical and chemical properties. For example, BVDV and Sindbis virus can be used in HCV studies. Based on an appropriate choice of model viruses (using for example both non-enveloped and enveloped viruses, as well as viruses known for their low resistance to physical and chemical inactivation and viruses known for their high resistance) it is hoped that protection from potential emerging viruses can be provided. These procedures are now part of the national and European regulatory arsenal.

c) better definition of the indications for transfusions and medicinal products of biological origin. The presence of a potential risk of infection with emerging infectious agents has prompted the medical community to spell out the clinical and biological situations in which the administration of a blood product is necessary. This has been done primarily through consensus development conferences bringing together specialists in transfusion, infection, surgery, pharmacology, virology and industry as well as representatives of patients' groups.

15. The scale of the epidemic, which soon became clear, and pressure from both patients' associations and a part of the health care community also contributed to bringing about a radical change in the way clinical trials are carried out and a major breakthrough in medical virology. The chronicity of the infection and the lack of reliable data on the long-term use of antivirals and/or immunomodulators soon prompted co-ordination of efforts and the definition of new methodologies to determine the efficacy of drugs.
16. This change, together with the advent of automatic gene amplification and the rapid establishment of public institutions to oversee basic and applied research (the Agence Nationale de la Recherche sur le SIDA (ANRS) national AIDS research agency has provided very effective leadership) introduced molecular virology in hospitals and streamlined the patient care system. In a few short years, molecular techniques have achieved outstanding reliability and proved effective in therapeutic monitoring. These methods are now also applied to Hepatitis C infections.

17. Overall, the explosive spread of HIV in both developed and developing countries against the relatively untroubled backdrop of the early 1980s (the Hepatitis B risk had just been brought under control) prompted an overhaul of the French blood transfusion system, a reorganization of the approach to the safety of medicines of biological origin, medical devices and transplants in all developed countries, a profound change in the doctor/patient relationship and a revolution in medical virology and clinical trials.

18. HIV infection has caused a lasting change in our approach to viral diseases. The lack of any real success in the search for a vaccine has served to encourage innovation in assessing biological risk linked to medicines and was also largely responsible for the recent creation of health safety agencies in France.

**Prions and public health**

19. Transmissible subacute spongiform encephalopathies (TSE), also called prion diseases, are linked to infection by agents of as yet unknown nature called unconventional transmissible agents (TSE agents) or prions. These diseases can be transmitted experimentally and are characterized by exclusive involvement of the central nervous system, a particularly long incubation period (which can exceed 40 years in man), the lack of effective therapy and the lack of a test to detect the disease during the lifetime of the patient. The disease is always fatal and has a subacute progression of a few weeks to a few months. These diseases remain rare in humans (prevalence: 1 to 2 new cases per million inhabitants per year).

20. The impact of these cases on public health reflects the intrinsic features of the agents that cause them. Prions have two main properties:

   a. they are highly resistant to conventional inactivation processes;
   b. they are able to cross the species barriers and induce disease or chronic carrier state in individuals belonging to a species different from their species of origin.

21. The most recent biological data show that TSE agents are most probably infectious units without a conventional genome (no DNA nor RNA are specifically associated with infection) and that they are virtually exclusively made up of protein. The prion theory postulates that the infectious agent is a host-encoded protein, PrP, which has acquired an abnormal three-dimensional structure without modification of its primary sequence. The pathological protein (PrPsc) is thought to become resistant to conventional proteolytic processes and to propagate its abnormality by modifying the conformation of normal PrP proteins expressed at the cell surface.
22. This new concept, supported by a large number of experimental findings, has caused a major upheaval in infectology and in our understanding of the respective roles of nucleic acids and proteins in physiopathology. It at least partly explains UTA resistance to conventional inactivation processes and thus the iatrogenic accidents observed in human medicine. Approximately 250 cases of medical or surgical accidental transmission have been observed to date, all involving contact with the central nervous system of the donor.

23. The appearance of bovine spongiform encephalopathy in the United Kingdom in the mid-1980s caused an economic disaster in the U.K. and continental Europe. Apart from its impact on animal health, the disease, which probably – though not certainly - originated when cattle were contaminated with a rare strain of sheep scrapie, was rapidly suspected of posing a risk to humans. Indeed, cases of species jumping had been observed in experimental prion diseases but no zoonosis belonging to this nosological group had ever been reported and scrapie had never been suspected of posing a risk to humans.

24. The first warning signs came when British cats were infected with the BSE agent in the early 1990s. The dangerous nature of the BSE agent was then confirmed when its probable spread to humans was reported in 1996. A number of observations and experimental data have to date supported BSE transmission to humans: 136 patients have developed a variant of CJD in the United Kingdom and 10 (of which 6 in France) outside the U.K.

25. It is therefore important to protect humans from exposure to the BSE agent. Effective protection involves lowering the incidence of the disease in cattle and removing the tissues known to be most infectious in animals from the food chain. A number of steps were therefore taken:

   a. to halt transmission to cattle via meat and bone meal made with ruminant tissues;
   b. to systematically screen for the pathological PrP protein in the central nervous systems of cattle in slaughterhouses before the animals enter the human food chain;
   c. to systematically prevent human and animal use of tissues recognized as capable of harbouring the highest infectious titres in known natural prion infections - the central nervous system and lymph tissues (concept of specified risk offal). This last measure has certainly been the most effective one in bringing the BSE epidemic under control and we should thank Richard Kimberlin for having urged it on the health authorities in the United Kingdom in the early 1990s before transmission of the BSE agent to humans was suspected.

26. The emergence of BSE also had an impact on medicinal products. In France in the early 1990s all cattle-based medications were reviewed for microbiological safety should the BSE agent be transmissible to humans. All medications for which the risk/benefit analysis was inadequate were then prohibited. This measure was extended to medical devices in 1994. The anticipation of the risk of BSE in humans can be considered a positive consequence of the drug safety approach adopted in the wake of the HIV epidemic.
27. Prions in fact had become a public health issue in the mid-1980s. The first cases of iatrogenic transmission of CJD through treatment with extractive human growth hormone (hGH) were reported in the United States and then in the United Kingdom in 1985. At the time, growth hormone was prepared from extract taken from pituitary glands harvested from cadavers in morgues. Three countries were affected - the United Kingdom, the United States and France. The relatively high incidence of these cases of CJD in France (more than 90 to date, i.e. more than 60% of all cases worldwide) prompted three measures:

a. a rapid switch to the use of recombinant growth hormone;
b. elimination of blood donations by subjects having prior exposure to TSE (neurosurgery, treatment with hGH, family history of genetic forms of TSE);
c. upgrading of sterilization procedures. Prior to 1995, the procedures for sterilizing surgical instruments had not been shown to be effective with TSE agents. The sterilization temperature was therefore raised to 134°C and the sterilization cycle time was lengthened. In addition, a hierarchy ranking of risks presented by patients and by surgical procedures was drawn up at the end of 1995. Modulation of procedures according to risk following a review by the medical team was amplified when data on vCJD showed that the lymphoid system was extensively colonized by the infectious agent (which is not the case in conventional CJD) and that the central nervous system was hence no longer to be considered the "only organ at risk".

28. In March 1996, 10 cases of atypical CJD (vCJD) were described in patients under the age of 40 (most under the age of 30) with no identifiable (genetic or iatrogenic) risk factors. This suggested possible transmission of the BSE agent to humans. Experimental data supported the hypothesis:

a. Inoculation of primates with the BSE agent reproduces the specific features of the new variant of CJD, especially with respect to its neuropathology;
b. An analysis of the electrophoretic profile of pathological PrP showed that vCJD can be clearly differentiated from other forms of Creutzfeld-Jakob Disease. This particular pattern (called Type 4), considered specific, is found in all cases where BSE is involved;
c. The biological properties of the prion strain which causes BSE match those of the vCJD agent and are very different from those of the agents causing conventional forms of CJD.
d. Genetically engineered animals in which the bovine PrP gene has been introduced are more susceptible to vCJD infection than genetically engineered animals with the human PrP gene.
e. Furthermore, the three-dimensional structures of the human protein and the bovine protein are strongly homologous.

29. One of the most specific features of vCJD is the wide distribution of infectivity outside the central nervous system (CNS). In contrast to conventional CJD, in which the infectious agent is only exceptionally found outside the CNS, in vCJD the abnormal PrP is always identifiable in the secondary lymphoid organs (spleen, tonsils, appendix, lymph nodes) of affected patients. The presence of the agent in the lymphoid organs suggests, given what is known about the circulation of
immunocompetent cells, that for public health purposes probable infectivity in the
blood should be assumed. This suggestion was recently supported by the
identification of low-level infectivity in the blood of sheep infected with natural
scrapie or experimentally exposed to the BSE agent. In "rodent" models, infectivity
can sometimes be detected in blood. The titre is low (10 IU/ml) and most of the
infectivity is associated with mononucleated cells.

30. As a consequence, leucodepletion of donated blood could in theory be one way to
fight against possible transmission of vCJD via the blood supply. It should however
be remembered that to date no infectivity has been found in the blood of patients with
natural vCJD. Steps taken to prevent blood donation by subjects having spent time in
the United Kingdom are therefore precautionary rather than preventative.

31. Numerous models have been drawn up to predict the number of future cases vCJD by
a variety of teams. The results vary with working hypotheses. However, the most
recent studies, based on different biomathematical approaches, give the number of
cases in the United Kingdom as no more than a few hundred over the next 20 years.

The impact of the crises: the health care system

32. The successive human and animal "health crises" have prompted major changes in
drug safety, medical devices and sterilization procedures. They also prompted a
greater public awareness of health safety and in particular food safety issues.
Operating procedures in the food-processing sector have been extensively overhauled.
Source monitoring has been reinforced, traceability introduced and the concept of risk
evaluation taken on board. These changes in attitude were particularly perceptible
among the public at large and contributed to the introduction of safety procedures
applying to food and health care products.

33. Operationally, a number of measures have been taken at national and community
level:

a. The Agence du médicament was set up in the mid-1990s charged, among other
   things, with analyzing risks related to medications of biological origin.

b. An Expert Group on Microbiological Safety was established under auspices of
   the Direction Générale de la Santé, with the remit of assessing the safety of
   medical devices.

c. The European Medicines Evaluation Agency (EMEA) was set up with one
   permanent working party to draft and provide ongoing updates of guidelines
   governing safety of medicines.

d. European scientific expertise was separated from the DGs for agriculture and
   industry. Between 1995 and 2000 the Multi-disciplinary Scientific Committee
   and then the Scientific Steering Committee (SSC) were set up within the
   European Union to report, alongside a number of specialized committees, to
   DG XXIV (Consumer Policy and Consumer Health Protection). The
   organization was designed in such a way as to ensure that all areas of health
   safety were covered by one or several expert committees, with consistency of
   proposals ensured by the SSC. Over the last few years, the consequences of
   BSE were the main focus of these committees; they produced several dozen
   scientific opinions, all made public, culminating in a precise and reasoned
appreciation of risks based on published scientific findings. Among the many
suggestions made by the SSC, the classification of countries by intrinsic risk
of BSE (the GBR) was certainly one of the most useful tools in effectively
combating BSE. This new approach to scientific expertise, separating it clearly
from policy and administrative decision-making and making it accessible to
the public, is probably the most important step taken over the last years in
terms of health safety.

e. Three health safety agencies were set up at national level: the Agence
française de sécurité sanitaire des aliments (AFSSA) food safety agency, the
Agence française de sécurité sanitaire des produits de santé (AFSSAPS)
health products safety agency and the Agence française de sécurité sanitaire
de l'Environnement (AFFSE) environmental safety agency. As a direct
consequence of the health crises at the end of the 1980s, these agencies
providing scientific expertise, as well as the Institut National de Veille
sanitaire (INVS) national health monitoring institute were set up by the
legislature which made them independent of decision-making bodies and
required that they be consulted a priori on all draft regulations falling within
their scientific remit. AFSSA, for example, has produced scientific expertise
of outstanding quality in a variety of areas ranging from nutritional balance to
microbiological risks. Its independence is clearly perceived by the public,
which sees in it an efficient structure which is economically and politically
neutral. The agencies use internal and external expertise. Calls for nominations
to the committees of outside experts received a strong response from the
scientific community. Furthermore, the presence of highly-qualified scientists
within the agencies is a crucial advantage in ensuring the consistency of their
operations and in interfacing with the public authorities.

f. Wide-ranging research projects were initiated on health issues and in
particular on prions, for which funding had been negligible prior to 1995. This
pro-active research policy was carried out at European level (through specific
BSE programs and more recently in the 6th PCRD) and at national level
through the creation of a concerted action (GIS) bringing together several
ministries and the research institutes, which has its own funding and is
charged with co-ordinating and expanding research into prion diseases. The
National AIDS research agency, set up at the end of the 1980s, for its part took
charge of overseeing research programs and clinical trials in the area of HIV.

g. The scientific and medical community on the one hand and health-care
workers and the public on the other became aware of the need for strong,
independent and publicly accessible scientific expertise to provide a coherent
and up-to-date approach to the major health safety issues.

Conclusion

34. The various segments of society seem to have become aware of health risks only
relatively recently. The public has called not only for a regulatory and legislative
framework capable of preventing new risks from arising, but also for effective citizen
participation in preventing the risks and managing their medical consequences. This
has been implemented at both national and European level, the most recent example
of this change being the establishment of the European Food Safety Authority in
2003.
35. The attitude of the citizen toward risk in general and toward the medical community changed more between 1985 and 2000 than it had over the 50 preceding years. The availability of information, the growing perception of science as relatively unable to provide overall solutions to health and food safety issues, and certainly the growing influence of European institutions were largely responsible for this greater public awareness of the consequences of the health crises of the 1980s and 1990s. This has often entailed a demand for a "precautionary approach", with the distinction between precaution and prevention not always clear in the public mind.

36. Be that as it may, if the public demand for greater health safety is to be effectively and efficiently met, there is a need for:

   a. genuine risk education,
   b. the establishment or continuation of \textit{ad hoc} scientific evaluation bodies that are independent of management structures;
   c. the creation of a European structure on emerging or re-emerging diseases;
   d. acceptance by the public of the economic costs of health safety and of the idea that economic and sociological considerations should be taken into account when establishing public health risk priorities.