epidemic. The blood components were 5 concentrated RBC units (all leukoreduced) and 3 PLT concentrates (2 leukoreduced). For donations made after 1994, 7 recipients were traced, of whom 2 were still alive. Twelve plasma donations were used for fractionation.

The third case (13th in the series, reported in October 2004) was a 48-year-old man who donated blood between 1991 and 2004. The components were one fresh-frozen plasma (FFP) and 15 concentrated RBC units (half of them leukoreduced). All 16 recipients were identified, of which 6 were alive.

In total, these 3 donors account for 42 recipients of RBCs or PLTs, of whom 16 were alive at the time of the investigation: 2 of these, transfused before 1984, were not informed, but 14 were notified because they received transfusions between 1991 and 2004. To date, none has presented with symptoms of vCJD. None of the deceased recipients were tested for evidence of infection, because all died several years before the diagnosis of vCJD in the donor. There were clearly more recipients of fractionated plasma products prepared from plasma from the affected donors. Two of the donors had given plasma destined for fractionation in the period 1991 to 2004 (10 donations in one case, 12 in the other). These 2 donors accounted for around 50,000 recipients: 2000 for treatment of chronic disorders (hemophilia, immunodeficiency), the rest for occasional treatment (albumin, immunoglobulins).

In response to the first three cases of blood donors who later developed vCJD, the following measures were put into place in France:

- Immediate recall of in-date fractionated plasma products and labile blood components prepared from these donors. When the illness was discovered in the donor, blood products had almost always already been transfused, but this strategy allowed the following actions.
- Information to the prescribers of the labile blood components implicated in the investigation.
- Direct and personal information to the recipients of blood components (except those transfused before the epidemic); exclusion of all recipients as donors of organs, tissues, and cells (they were already excluded from blood donation because of their history of transfusion); and finally, putting in place long term clinical follow-up.
- A decision to not inform individual recipients of fractionated plasma products, except hemophiliacs who had received Factor (F)VIII or F IX produced from the affected donations.
- Information aimed at the general population and at health professionals about the possibility of transfusion transmission of vCJD.

The information given to the blood transfusion recipients by their doctor proved more difficult than that given, more than 20 years previously, to the first blood donors to be found "LAV positive," who were already aware of the large number of uncertainties at the time about the prognosis of infection by the agent responsible for AIDS. Those who supported not informing recipients of the risk of prion transmission through blood transfusion use the following arguments: it is not possible to quantify the absolute risk, because of a number of unknowns and the absence of a diagnostic test; the existence of preventive measures applied in recent years against the risk linked to labile blood components; the major psychological harm resulting for such information, which can only generate major anxiety; absence of any diagnostic or prognostic tests (except for codon 129 status); and finally, lack of any prophylaxis or treatment. On November 4, 2004, the National Ethical Consultative Committee of France (CCNE) confirmed its position expressed in 1997: to not worry without benefit, notably where no preventive action is available, and to take into account the risk of excluding a patient from health care in the name of the precautionary principle. Finally, the CCNE insisted on the need for complete traceability of donations of blood from donors who had subsequently developed vCJD.

Those in favor of informing recipients of the risk pointed out the need to inform them that they could no longer donate (in principle, because they had been transfused, the subjects were already excluded permanently from blood donation), but also that the patients had "the right to know," imposed by French law on March 4, 2002, which puts an obligation on the doctor to alert the patient to all "newly identified risks," even if the degree of the individual risk is not quantifiable and there is no available diagnostic procedure and no means of prevention. Another factor favoring informing recipients is to reduce the risk of secondary spread to health care workers, dentists, and other patients. The French circular number 138 of March 14, 2001, defined the management principles of the risks of transmission of "nonconventional transmissible agents" during medical and surgical procedures and had classified the recipients of labile blood components in the category of patients at individual risk of contamination by the vCJD agent. For all these reasons, in France, it was ultimately decided to inform patients at high risk of prion infection.

PRECAUTIONARY MEASURES FOR DONORS AND LABILE BLOOD COMPONENTS IN THE UK AND FRANCE

Since the removal of infected beef products from the food chain, a public health measure taken to protect the general population, precautionary measures to reduce the risk of transfusion transmission of prions were implemented in the UK and France in line with advances in epidemiologic knowledge. Some were put in place before the emergence of the first case of transfusion-associated vCJD, primarily to reduce the risk of transmission of other forms of CJD and in particular the iatrogenic forms. The first case of transfusion transmission of vCJD provoked the health authorities in the UK and France to take new and complementary risk reduction measures. Along with the exclusion of at-risk donors, the introduction of leukoreduction has contributed to the reduction of the infectious load in prion transmission by blood[56] (it has been shown that this could reduce the infectivity of whole blood by almost 50%[57]). Despite this, as the cases of vCJD transmission by blood transfusion observed in the UK were all due to nonleukoreduced blood components, it could be concluded that the decrease is by definition accounted for by leukoreduced blood components, and above all that it has been established that the white blood cell (WBC) layer does not contain all the infectivity: an equal amount of infectivity exists, we now know, in plasma. Leukoreduction therefore appears a necessary measure, but certainly not sufficient.

Table 1 lists, in chronological order, the precautionary measures, specific or nonspecific, put in place in the UK[58,59] against the risk of transfusion transmission of vCJD. In France, the precautionary measures followed the same pattern in a number of complementary actions. The circular of September 23, 2005,[60] concerning the reports of the first probable British cases of transfusion transmission of vCJD and the first case of a French donor who developed the illness, raised the issue of secondary transmission by transfusion of labile blood components or by use of surgical instruments or endoscopes on patients who had received transfusions of blood components originating from donors who later developed vCJD. The successive measures instituted in France and including those taken for the other forms of CJD before the emergence of vCJD, are shown in Table 2.

TABLE 1. Preventive measures in the UK against the transfusion risk of vCJD

1997	Recall and discard of labile blood components and of plasma derivatives obtained from donors who later developed vCJD.
1998	Importation of plasma destined for fractionation from non-UK sources.
1999	Leukoreduction of all labile blood products.
2002	Importation of FFP for recipients born after January 1, 1996.
2004	Permanent donor deferral in case of transfusion after January 1, 1980.
2005	Importation of FFP for recipients age less than 16 years.
	Permanent donor deferral in case of transfusion anywhere in the world after January 1, 1980.
	Permanent deferral and notification of donors whose donations have been transfused to recipients who later developed vCJD.
	Progressive replacement of PLT pools with apheresis (single-donor) PLTs. Apheresis PLTs recommended for children age less than 16 years.

TABLE 2. Preventive measures in France against the transfusion risk of vCJD

1992-1995	Permanent donor deferral in case of treatment by injection of growth hormones of pituitary origin.
	Permanent donor deferral in case of history of neurodegenerative disease.
	Recall and discard of labile blood components and batches of plasma products containing plasma from donors who later developed sCJD, fCJD, or iatrogenic CJD; having a history of fCJD; or having been treated with hormones of pituitary origin.
	Permanent donor deferral in case of history of neurosurgery.
1997	Tracing of recipients of labile blood components collected from donors who later developed CJD.
	Permanent donor deferral in case of transfusion of graft.
	Recall and discard of labile blood components and plasma products obtained from donors who later developed vCJD.
1998	Leukoreduction of cellular blood products for a residual level $<1 \times 10^6$/unit.
2000	Permanent deferral of donors who lived in UK for 1 year or more between 1980 and 1996.
2001	Leukoreduction of all plasma (FFP or plasma destined for fractionation) to a residual level $<1 \times 10^6$/unit.
	Residual WBC level $<1 \times 10^4$/unit for plasma not destined for fractionation.
	Reduction of volume of plasma in PLT components through use of PLT additive solution, potentially reducing an infectious load.

Information for doctors, recipients, and donors.

One difficulty with the current situation is that individuals incubating vCJD but still asymptomatic will not know they are at risk and may be donating their blood. This is relevant as those affected to date with vCJD have been relatively young and could donate their blood several times per year, for many years. In these circumstances, the only specific preventive measure against prion contamination of blood transfusions would be to rely on a diagnostic blood test for qualification of donors, or a general measure which could prove absolute efficacy (while one waits for prion filters), or both.

In the prevention of any transfusion risk, an equilibrium between the deferral of at-risk donors and the need for blood components is necessary. Being the most exposed country, the UK has taken major measures against prion transmission by blood transfusion, such as the importation of all plasma for fractionation.[61] Although leading to the exclusion of numerous blood donors,[62] these measures were imposed by the "precautionary principle."[63,64]

Transfusion measures taken in other countries are essentially based on the exclusion of potential blood donors who have stayed in an "endemic" area. For example, the Canadian authorities took successively more stringent measures to exclude from donation individuals who became at risk through a stay in a country affected by the vCJD epidemic: in 1999, all people who had spent a cumulative period of 6 months in the UK since 1980 were excluded from donation; in 2000, it was the same criterion for a stay in France; in 2001, the duration of a stay in France or the UK was reduced to 3 months; and that of a stay elsewhere in Europe must not exceed a cumulative period of 5 years.[65,66]

After a case of vCJD in an individual who visited the UK for less than 1 month in the 1980s and who developed in 2001 an illness that led to his death in 2004, Japan also took precautionary measures for blood transfusion, considering that the patient had become infected in the UK, even though approximately 15 cows born in Japan have been identified with BSE. Having already excluded donors who had stayed more than 1 month in the UK, the Japanese health authorities took the decision to exclude all individuals who had stayed for even 1 day in the country between 1980 and 1996. One can see that prion infection and the precautionary principle have at least two common points: they cross all frontiers and spread in an unforeseen manner.

THE VARIABLES OF RISK OF TRANSFUSION TRANSMISSION OF PRIONS BY LABILE BLOOD COMPONENTS

At this stage of medical knowledge, it is clear that all the elements of risk for transfusion transmission of prions are not clarified. Certain elements are however identifiable:

1. The number of labile blood components received by the patient and the date of their production in relation to the dates of the epidemic and to the application of precautionary measures (exclusion of at-risk donors, leukoreduction, etc.).
2. The prevalence of infection in blood donors: a great uncertainty exists about this prevalence that will depend upon that in the general population who were exposed through diet in the UK and in France. A calculation taking into account the higher end of the estimate of between 6 and 300 persons infected in the general French population and imagining these 300 cases among the 36 million subjects who are in the age range to be blood donors (18-65 years) and eligible to be donors, and assuming that they could be infective during the whole incubation period, results in a prevalence of 1 in 120,000: that is approximately 8 infected individuals per 1 million donors, which is close to 11 infected donations per year—in a *worst case scenario*.[67] In a recent reevaluation, the number of expected vCJD cases in France was revised downward (maximum of 100 cases instead of 300), leading to an estimate of 1 donor infected in 1/360,000. The equivalent calculation in the UK gives a prevalence of 1 in 10,000 donors, although better estimates may become available in the UK with results from the National Anonymous Tonsil Archive testing that is currently in progress.
3. Infectivity of a labile blood component with regard to prions is still ill understood. One measures and refers to an "infectious dose," defined as the minimal dose capable of transmitting the infection in an animal model for the mode of contamination given. At present, the infection of a unit of blood depends on two factors:
   - The stage of infection in the donor: the level of circulating prion and thus the infectivity certainly increases with the duration of the incubation period.[68] This ignores the delay before which the blood of

the infected subject becomes infective for the recipient of the blood: an infected donor, donating during the early part of the incubation period, may not be infectious to a recipient. According to animal studies, blood infectivity can be demonstrated at least at the start of the second half of the incubation period and perhaps also earlier (the infectivity of blood precedes the presence of pathological prion in the brain and the organs).[68] Even though experiments suggest that infectivity will be absent or minimal during the first third of the incubation period, caution dictates, in the current state of knowledge, that a labile blood component originating from a donor in the incubation period contains at least one infectious dose.[69] As many years have passed since the peak of the dietary epidemic, infected individuals are no longer in the initial stages of infection. The paradox could be that even though the number of infections is no longer increasing, the number of infectious subjects could still increase over time.

- Second, the efficacy of leukoreduction for cellular components and for plasma: leukoreduction of hamster blood contaminated with a scrapie prion removed only a little less than half (42%) of the infectivity present, because the infectivity divides almost equally between the WBCs and the plasma.[57,70,71] Leukoreduction may therefore be less effective than originally calculated. As demonstrated in studies based on experimentally infected rodent blood, total blood infectivity will be, during the asymptomatic phase, from 20-30 IU per mL,[35] and the distribution in the compartments of blood is in the order of 30 percent in the buffy coat and 50 percent in the plasma.[71] The presence of RBC and PLT infectivity has not been established in a formal manner: it seems at any rate to be little or none.[72,73] Thus, after the implementation of leukoreduction of labile blood components (which must have a residual WBC count of $<1 \times 10^6$/unit), the infectivity of RBC or PLT components is dependent on the amount of residual plasma. Use of optimal additive solutions for cellular components helps to reduce the quantity of plasma and therefore the infectious dose in the case of an infected blood component.

4. Recipient methionine homozygosity at codon 129 has an impact on the risk of developing illness, with perhaps a hierarchy of risk, moving in descending order from MM homozygotes to MV heterozygotes to VV homozygotes. Furthermore, nonhomozygosity for MM does not appear to confer absolute protection from infection, as indicated by the second UK recipient case (an MV heterozygote, nonetheless infected through the transfusion route) and in experimental animals.[13] What is certain is that the clinical outcome of transfusion transmission appears to be greatest for MM homozygotes, since they alone of the "exposed" population at risk have developed the disease.
5. Finally, the length of the incubation period, an essential factor and of which much is currently unknown and to which must be added two important parameters: the age of the recipient and the posttransfusion survival, which is heavily influenced by deaths due to the underlying illness in the initial years after the blood transfusion.

PRION FILTERS

Specific prion reduction filters applicable for certain labile blood components have been undergoing validation. The first donations processed with these prion filters demonstrated their capacity to reduce spiked infectivity of blood by three logs, which would without a doubt make a significant contribution to reducing transfusion risk.[74] These filters have been produced by two companies with a view to use for RBC preparations: application to PLT preparations and to plasma await further work. The validation work has been carried out on the Pall leukotrap affinity prion reduction filter, integrated in the filter CompoSafe Pr Fresenius,[75-77] and the TSE affinity ligand of the pathogen removal and diagnostic technologies, integrated in the P-Capt MC (MC for Macopharma) filter.[78] Changes were made to the Pall filter after the initial validation, which affected performance and led to its withdrawal. A new combined leukoreduction and prion removal filter from the same manufacturer is now under development. These affinity filters are assumed to remove all detectable traces of infection in a contaminated unit and to reduce infectivity by transfusion. This capacity has been demonstrated by a study based on inoculation, in hamsters, of leukoreduced whole blood taken from animals infected by a TSE. When the blood was treated with passage over a filter, no hamster became infected. When the blood was not filtered, some hamsters developed illness associated with the presence of prions in tissues.[79] Nevertheless, although the potential of these filters has been demonstrated by experimental infectivity transmissions in animal models, their efficacy in the prevention of

human transfusion transmission remains to be validated.[80] Indeed, the amount and the form of the pathological prion circulating in different human blood components may differ from that in an animal infected in an experimental manner, in particular from brain extracts. These artificial situations cannot reproduce exactly the qualitative and quantitative characteristics of the human prionemia. The most infectious aggregates of pathologic prion protein are those that are formed of 14 to 28 molecules,[81] but the size of circulating aggregates in the blood remains unknown. Furthermore, the consequences of using prion reduction filters on blood constituents (notably in the maintenance of PLT function) and on plasma proteins is totally unknown.[82] Chief of the possible consequences are the risk of neoantigenicity and induction of inhibitors.

A MUCH-AWAITED DIAGNOSTIC TEST

Lacking nucleic acid and not provoking any immune response by the infected host, the pathologic prion cannot be detected by molecular or serologic methods usually used in viral diagnosis. Furthermore, research for indirect markers has, up to now, reached a dead end.[83-85]

In asymptomatic or symptomatic infection, the most useful diagnostic test will be based on detection of the pathologic prion in the blood. However, the form that the prion takes in the blood is different from its form in the central nervous system. PrP^{sc} has an aggregated form in the brain and a much more soluble fraction in the blood: that difference could influence the effectiveness of diagnostic tests, the majority of which are based on the capacity to detect the cerebral form. Furthermore, the pathologic form only represents part of the circulating prions, but it is this pathologic form that the test must detect. Most of the diagnostic tools developed up to now depend on the physicochemical differences in the two forms of prion, the normal and the pathologic, in particular on the resistance of the pathological form to proteinase K.[11,86-90]

A large number of unknowns relating to the transmissibility, epidemiology, and natural history of prion infection will no doubt be resolved when one or several diagnostic tests, having the necessary characteristics of sensitivity, specificity, and reproducibility, become available and usable on a large scale.[59,91,92] Major efforts are presently being made to develop such tools, which could be used in the screening of blood donations and would help to reduce even further the risk of transfusion transmission of prions. These tests should, nevertheless, meet strict criteria:[93,94]

1. A very high sensitivity, to detect an infectious load that may be very low in asymptomatic subjects, because a low level of PrP^{sc} in circulating blood is likely to be infectious for recipients of blood components.
2. High specificity is essential, since the normal protein is present in the circulating blood.[95] False-positive results could have disastrous consequences, in terms of notifying individuals whose blood donation had been concluded "positive," not to mention the unjustified deferral of a large number of donors. For other infections, every reactive result obtained through blood donation screening tests must be verified by a confirmatory test to separate true-positive results from false-positive results. At present, it is not known if a true confirmatory test will be available, whether the solution for prions will be two screening tests performed simultaneously, or if one will be used for "confirmation" of a positive result by the other. On the problem of specificity, it has been calculated that, if a diagnostic test having a 99 percent sensitivity and an equivalent specificity was applied to the screening of blood donations in a population having a prevalence of vCJD of 1 in 10,000 (which is the estimate for donors in the UK), 99 individuals would be detected in the incubation phase of the infection and would correspond to "true positives" for 1 million tested donors, but 10,000 donors would give a false-positive result. On the other hand, there would only be one false-negative result in 1 million tests.[96] In France, where an estimate of prevalence is 1 donor infected in 360,000, fewer than 10 carriers of the variant would be detected, but the number of false-positive results would be just as high as the UK: 10,000 per 1 million donors, who would not be allowed to give their blood and who would need to be informed of their biologic status.
3. Finally, these tests will have to be reproducible, usable on a large scale, and able to be carried out within a time scale that is compatible with the shelf life of PLT components, criteria that have been required (and obtained) for nucleic acid testing in transfusion.

The lack of a test with the above-mentioned characteristics has major consequences: the impossibility of deferring from blood donation all those who are carriers of vCJD and the necessity of basing the screening of donors and of blood donations on nonspecific or partially effective measures such as existence of a risk factor in the donor, leukoreduction of blood donations, and so forth; the impossibility of detecting infected recipients and of testing at-risk recipients; the difficulty in collecting data about the mean duration of incubation of the illness; and in France

and in other countries, the impossibility of rehabilitating donors excluded because of a stay in the UK during the affected years (all the more because, among the cases of vCJD identified in France, such a history has been found only once and it becomes a paradox to exclude donors on the pretext of a visit to the UK when almost all the French patients who had the illness were infected in their own country). It would be necessary, furthermore, to take care that the positive effect of such a "rehabilitation" for some donors was not offset by a negative effect, by announcing, in the media, the use of a specific transfusion screening test. This could raise concern in the donor population, of learning, through giving blood, that they carry the infectious agent of an illness for which there is no preventive or curative treatment.

While awaiting validation, and preceding their potential use in detecting donors who are infected by vCJD, the first tests could be usefully applied in studies of sample repositories, to determine the spread of the epidemic in the overall population and in the transfused population. Assessment of the prevalence of vCJD in donors and recipients of blood, as well as its transmissibility through plasma products, could be carried out via anonymous plasma samples of matched donors and recipients. This is one of the possibilities provided by the repository presently undertaken on a European scale, called "BOTIA" (Blood and Organ Transmissible Infectious Agents).[97] Indeed, for obvious ethical reasons, one cannot use imperfectly validated tests on nonanonymous samples.

Meanwhile, the absence of a diagnostic test and strong uncertainties about a transfusion epidemic of vCJD requires maintenance of the preventive measures established by the UK, France, and other countries. If a specific test is used in transfusion in the future, there will be the opportunity to consider relaxation of these measures.

UNCERTAINTIES

An illness whose pathogenicity is not well known, with an uncertain prevalence of the infectious agent in at-risk groups and in the general population, the absence of a screening test, infectiousness and duration of incubation poorly defined, and the absence of any therapy, make up the elements that influence the transfusion risk of vCJD and handicap its prevention. Many questions have no answers, and the order in which we enumerate them probably does not correspond to the sequence in which solutions will be found:

1. After the end of the UK dietary epidemic and after the peak of the vCJD epidemic in 1999, will there be a second peak of transfusion origin? Up to now, the epidemic has remained relatively limited: approximately 200 cases worldwide, of which three-quarters have been in the UK. The initial pessimistic hypotheses on future number of cases have been revised downward. Furthermore, the peaks that followed the initial peak of CJD cases linked to injection of contaminated growth hormone were smaller and smaller, as if patients of other genotypes were less susceptible to infection and/or to the development of clinical illness. It is not known if the same will happen with vCJD, but the hypothesis of a secondary transfusion epidemic, with reamplification of the phenomenon through asymptomatic carriers of the prion, cannot be excluded. Nevertheless, it is now 14 years since the first cases of vCJD occurred, and no evidence of clinical cases in heterozygotes has appeared, in contrast to observations in the growth hormone epidemic. Finally, intraspecies transmission of prions induces, compared to interspecies transmission, a shorter incubation period and increased effectiveness of transmission. This could cause a larger outbreak of infection through transfusion than through contamination by food.
2. What is the prevalence of infection in the general population of the UK and in France, and how many potentially infected donors are there? The results of a retrospective British study on the prevalence of vCJD in surgical tissues from appendectomies and tonsillectomies pointed in the direction of a much higher prevalence of asymptomatic carriers than was implied by the known number of symptomatic cases. Furthermore, since, in the British MV transfused recipient carrying the variant, PrP^{res} was only detectable in the spleen and the cervical lymph nodes, and not in the appendix or the tonsils, this retrospective epidemiologic study based on detection of the pathologic prion in the appendix could have underestimated the size of the epidemic in the general population.
3. What are the kinetics of the appearance of circulating prion during the incubation phase? For estimation of the transfusion risk, the working hypothesis is that of blood infectivity and thus potential transmissibility throughout this phase, but the prion level in circulating blood may be too low, in the first months or first years of infection, to transmit infection by transfusion.
4. What is the effect of the current precautionary measures in transfusion, especially leukoreduction? The margin of safety that this measure gives is unknown. Has a reduction in infectivity prevented, or will it prevent, some transmissions by blood components? Up to now, the most feared contradiction would be the appearance of vCJD in a recipient transfused solely with leukoreduced components. Such a finding has not yet been reported.

5. Do non-MM subjects (that is, 60% of the general population) have absolute resistance to the disease, or might they develop it after a longer period of incubation? This latter instance would imply a second wave of the epidemic, which might, furthermore, be partially masked by other causes of death.[98] But in both situations, infected asymptomatic subjects would not be less infectious if they donated their blood, and recipients could become symptomatic if they have the MM status. Such a situation would be epidemiologically disastrous: an MV or VV infected donor could transmit vCJD to any number of recipients and not become ill him- or herself, but the recipients would develop illness if they are MM. Such circumstances have been observed in viral transfusion transmissions, notably in infection by HIV, where an infected recipient could develop symptomatic illness several years before the donor. In these conditions, donors who are carriers of vCJD but do not develop the illness because of a protective genotype at codon 129 would not be identifiable without a specific diagnostic test, except by transfusion investigations showing their common donor status in two (or more) recipients infected by vCJD who had developed the illness because of a nonprotecting genotype. Such studies would be critical as the only ones capable of identifying a regular, infected donor and of interrupting a chain of transmissions by transfusion. One can perceive to what extent the deferral of transfused patients from giving blood is an essential measure in breaking a "contamination cycle" between the donor population and that of recipients. Implemented several years ago, this precaution has probably avoided several transfusion transmissions of vCJD, even if a German study, based on a mathematical model, has concluded that the effect of this strategy is minimal: arguing that the majority of donors were infected from dietary sources and, having never been transfused, would not be excluded from blood donation.[99]
6. How many donors and recipients will develop vCJD during the next few years, each time leading to transfusion lookbacks and investigations? In the TMER study, among recipients of blood collected from vCJD-infected donors, the proportion of recipients who developed the illness has appeared high in a relatively short period of time (less than a decade), taking into account that the truly at-risk group was reduced by the genetic status of codon 129.
7. Will the threat of transfusion transmission of prions be limited solely to the UK and France? The description, in other countries such as Spain and Saudi Arabia, of cases of vCJD with a past of blood donations, suggest that the problem has now taken on an international dimension, including, and above all, in its aspect of transfusion safety.

CONCLUSIONS

The possibility of a blood component recipient developing vCJD 10, 20, or 30 years after transfusion, and that of a regular donor developing it after the same amount of time, are two situations that will not find any solution except with the help of a transfusion traceability almost as prolonged as the human life span. The basic danger of the past dietary epidemic is now a problem of chronic asymptomatic carriers who donate their blood or can transmit the infection via medical devices used in surgery or in endoscopies,[100] creating and thus enlarging a secondary wave of epidemic.

An essential notion is that of protection provided by leukoreduction of blood components. In a worst-case scenario, where cases of vCJD would show up in recipients who have been exclusively transfused with leukoreduced blood components and thus infected by the residual plasma, the only solution, in the absence of a biologic test for the screening of blood donations, would be to have recourse to prion filters, if the question of their effectiveness and harmlessness is resolved, or to only use washed RBCs, with all the accompanying logistical and financial concerns[101]—even if a partial reduction of prion level through leukoreduction would help to reduce the number of infected recipients and/or to induce a longer incubation period (in the hypothesis that this period would be proportional to the original contaminating infection).[102]

Many professionals in the field of transfusion infection are betting on the efficacy of prion filters, while acknowledging that demonstration of their clinical efficacy remains difficult for reasons we have already described and which are dominated by the absence of a diagnostic test usable on a large scale. At present, a decision to use these filters is problematic and leads to as many questions as not using them. In addition, perfecting a screening test that would be applicable for blood donations will raise a no less difficult question: filter or test? Filter and test?

Procedures for the inactivation of infectious agents in labile blood components will probably be implemented, but since they are aimed at the nucleic acids of these agents, they will not be effective against prions. For this reason,