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販売名（企業名）						

研究報告の概要

米国では，有効性の高い抗レトロウィルス療法が90年代に導入されて以降，AIDSの危性に対する人々の関心が低下している。この問題は，南部農村地方出身のアフリカ系アメリカ人のみならず，ヒスパニック系の若年層，および低所得層において特に顕著である。白人アメリカ人よりもHIV感染率がはるかに高いアフリカ系アメリカ人はリスクの高い性行動をとっているにもかかわらず，十分な保険医療を受けていない。HIVに感染したアメリカ人の4分の1が感染しているということに気付いていないことから，自らのHIV感染状態についての認知度を高めることが感染予防への大きな課題である。例えば，母子感染予防を目的として妊婦に対する定期検査の一環としてHIV検査を実施することや，服役者に対する検査などが予防策として挙げられる。また，移動検査車など医療施設外での簡易検査の可能性を探ることも有用であろう。政策面では，薬物常用者間での注射針およびシリンジの交換に関する教育プログラムに止まらず，感染者に対するケースマネジメントプログラムと併行して薬物中毒者に質の高い治療を提供するなども検討すべきであろう。コンドームの適切かつ継続的な使用に重点を置いた予防策も講じるべきである。最後に，HIV感染の高リスク地域においてHIV予防策を支援するための新たな指導者の輩出が急務である。

使用上の注意記載状況・その他参考事項等

The impact of male-to-male sexual experience on risk profiles of blood donor Sanchez AM et al. TRANSFUSION, 2005;45:404-413

報告企業の意見	今後の対応
アフリカ系アメリカ人はAIDS高リスク集団として考えられ，供血者のスクリーニングでは人種的要因を考慮する必要性を示唆している。現在，弊社の血漿分画製剤では，60日以上の血漿保管，プール血漿に対するNAT検査の実施および血漿分画製剤の製造工程においてウイルスの除去化が行われており，血漿分画製剤を介した理論上のHIV感染リスクは極めて低いと考えられる。	現時点では，弊社の血漿分画製剤の添付文書，採漿方法および製造工程に対して新たな安全対策上の措置を講じる必要は無いと考える。引き続き関連情報の収集に努める。

POLICY FORUM

PUBLIC HEALTH

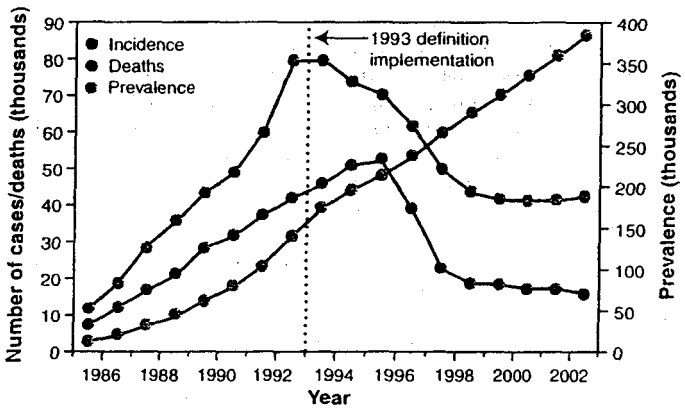
Whatever Happened to the U.S. AIDS Epidemic?

Harold Jaffe

Although more than one-third (36%) of Americans believe AIDS is the "most urgent health problem facing the world today," ranking second behind cancer (41%) (*1*), concern about HIV/AIDS in the United States has been falling. In national surveys, the proportion of Americans who consider HIV/AIDS to be the "most urgent health problem facing this nation today" has decreased from 38% in 1997 to 17% in 2002" (*2*). The Centers for Disease Control and Prevention's (CDC) budget for domestic HIV/AIDS programs increased by only 5% from 2001 to 2004, less than the rate of inflation (*3*).

Enhanced online at www.sciencemag.org/cgi/content/full/305/5688/1243

Some of the decreasing interest in the domestic epidemic is understandable. With the increasing availability of highly active antiretroviral therapy (HAART), annual AIDS cases and deaths have fallen dramatically (see the figure). AIDS is now viewed by many as a chronic disease for which survival can be measured in years rather than months. As the profile of persons with AIDS has gradually shifted from white middle-class gay men to poor African-American and Hispanic residents of the inner city and rural South, and as AIDS "celebrity deaths" become fewer, the general public appears to find the epidemic less alarming. Yet there are still reasons for concern.



Number of AIDS cases, deaths, and persons living with AIDS in the United States. Numbers are adjusted for reporting delays. All surveillance data are from (*23*).

The Problem

Since the epidemic was recognized in 1981, it has killed more than half a million Americans, a total exceeding all American combat-related deaths in all wars fought in the 20th century. Despite great advances in treatment, HIV/AIDS is the second leading cause of death in African Americans between the ages of 25 and 44 years. The number of Americans living with AIDS also continues to rise and is now approaching 400,000 (see the figure). Because of variability in state reporting laws and the difficulty in distinguishing between recent and long-standing infection, precise national HIV incidence data are not available. However, the CDC estimates that about 40,000 Americans become infected each year (*4*). This figure is not believed to have changed over the last decade. The mean annual expenditure for care of an HIV-infected patient in the HAART era is estimated to be about $18,000 (*5*).

A major challenge to prevention is to increase the number of persons who know their HIV infection status. Without this knowledge, infected persons cannot know they may be transmitting the virus to others and will not receive HIV treatment and care. Yet of the estimated 850,000 to 950,000 infected Americans, about a quarter are unaware of their infection (*6*). Even when persons do seek testing, it is often late in the course of their infection. For example, during 2000 and 2001, 37% of persons diagnosed with HIV either had AIDS at the time of their first positive test or developed an AIDS-defining condition within a year of that test (*7*). To some extent, this problem reflects the reluctance of health care providers to offer routine testing to persons at risk for HIV infection or living in high-prevalence areas. Early in the epidemic, there was strong opposition to HIV testing because of perceptions that the test was inaccurate and the confidentiality of results could not be maintained (*8*). Many providers also considered the requirements for extensive pretest counseling burdensome. Moreover, because treatment was not available, there was little incentive to learn one's infection status.

Although the proportion of men who have sex with men (MSM) among reported AIDS cases has decreased, this population still accounts for the largest number of persons with AIDS. Further, in the 30 states with long-standing reporting of HIV infection, diagnoses among MSM increased 17% from 1999 to 2002, while remaining stable in other risk groups. Outbreaks of infectious syphilis in MSM, about half of whom are HIV-infected, indicate ongoing high-risk behavior. The continuing HIV epidemic in MSM remains a prevention challenge, with no easy answers. Many factors may be contributing to these behaviors (*9*). One likely explanation is that HIV/AIDS is no longer viewed as a fatal disease. Older MSM may also be suffering from "prevention fatigue," meaning that they are simply tired of hearing the same prevention messages. For younger MSM, the lack of apparent illness in peers along with the belief that HIV/AIDS was only a problem for a past generation may contribute to risk-taking behavior. Other factors contributing to unsafe sex may include the use of recreational drugs, particularly crystal methamphetamine (*10*) and easy access to anonymous partners through the Internet (*11*).

Among African Americans, the epidemic poses particular prevention challenges. Overall, AIDS case rates are 10 times higher in African Americans than in white Americans. Reasons cited for these high rates include poverty, substance abuse, increased rates of other sexually transmitted diseases that facilitate HIV transmission, and lack of access to and utilization of health care. Particularly hard hit have been African-American women and youth, who account for about two-thirds of AIDS cas-

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es in women and teenagers, respectively. Many of the young women are being infected by older male sex partners. Bisexual men may also be playing a role in transmission to women. In one study of HIV-infected MSM, 34% of African Americans acknowledged having sex with both men and women as compared with 13% of non-Hispanic whites (*12*).

Some Solutions

To address some of the prevention challenges, CDC announced a new public health initiative in 2003: *Advancing HIV Prevention: New Strategies for a Changing Epidemic* (*4*). Much of the initiative is focused on increasing knowledge of infection status by making HIV testing a routine part of medical care and providing new models of testing outside of medical settings. The initiative also emphasizes prevention programs for infected persons, including strategies to decrease mother-to-child HIV transmission. In the prenatal setting, for example, voluntary "opt-out" testing (notification that an HIV test will be included in a standard battery of prenatal tests unless refused) is now a recommended approach to prevent perinatal transmission (*13*). Pretest counseling need not be extensive (*14*).

A key technical advance for increasing knowledge of infection status has been Food and Drug Administration (FDA) approval of a rapid HIV antibody test that can be performed outside the laboratory and provide results in about 20 minutes (*15*). The use of this test is now being evaluated for persons receiving care in medical settings, such as emergency departments, as well as in nonclinical settings, such as mobile outreach vans. Persons with negative results can be told they are not infected. Those with positive results are told that they are likely infected and are asked to return in a week or two for a confirmed result.

Progress in HIV prevention will also require identifying new prevention venues, such as correctional facilities. At any given time, about 2 million Americans are incarcerated in prisons or jails. At the end of 2001, 2.0% of state prison inmates and 1.2% of federal prison inmates were known to be HIV infected (*16*). Many other jail and prison inmates are at risk for infection upon release based on their histories of drug use or high-risk sex. In jails, where stays are typically only a few days, rapid HIV testing is feasible and can be linked to prevention and care services for those found infected. In prisons, where stays are longer, more comprehensive HIV prevention programs can be instituted. Making HIV prevention a priority in correctional settings will require both funding and a commitment from public health and correctional officials.

Advancing beyond the status quo may also require actions that have not been politically acceptable. For example, sharing of needles and syringes is the main route of HIV transmission among injection drug users, who still account for almost a quarter of newly reported persons with AIDS. However, access to sterile injection equipment is often limited by state laws that restrict sales of syringes, criminalize their possession, and limit the operations of needle and syringe exchange programs. Although exchange programs have been shown to reduce needle sharing (*17*) and are supported locally by city governments and community-based organizations, as well as internationally by the governments of many other industrialized countries, the use of U.S. government funds for these programs is prohibited. HIV prevention programs for injection drugs users should also include access to high-quality addiction treatment, along with prevention case management services for infected persons; such services are not always available or adequately funded.

The role of abstinence programs has also been politicized in the development of HIV prevention strategies. Abstinence, including interventions to delay the onset of sexual activity, clearly makes sense as a prevention strategy for youth, and has been shown to be effective in heavily affected countries, such as Uganda (*18*). However, the majority of American teenagers, over 60% in 2003, report that they have been sexually active by the time they are high school seniors (*19*). Additionally, the "abstinence until marriage" message has no meaning for gay and lesbian persons, for whom marriage is illegal in most of the United States. In contrast, prevention strategies emphasizing correct and consistent use of male condoms, a highly effective means to prevent HIV transmission (*20*), have been criticized (*21*).

New voices and community leadership to support HIV prevention are urgently needed. The dramatic upswing of HIV infections that occurred among MSM during the early 1980s was followed by an equally dramatic drop in incidence during the mid-to-late 1980s (*22*). This reduction occurred well before substantial federal or local funding for HIV prevention became available and almost certainly reflects prevention efforts within gay communities themselves. However, many of the leaders of those efforts have either died or are no longer active in HIV prevention. Although current activism largely has focused on access to therapy, more advocacy for prevention is critical. The message must be that prevention of HIV infection is of paramount importance, even though the infection is now treatable. Infected persons, individuals who know the burden of lifelong treatment with potentially toxic drugs, could be particularly credible spokespersons.

Similarly, more HIV prevention leadership is needed in the African-American community. Because of a variety of issues, particularly those related to racism, stigmatization, and homophobia, there has been some reluctance within this community to acknowledge the seriousness of the HIV/AIDS problem. For some, the epidemic may be just one more burden to bear. The black church and other faith-based entities, powerful social forces in the African-American community, can play critical roles in HIV prevention. Without political, community, and faith-based leadership, the problem will only become worse.

Americans should be proud that their country is now fully engaged in the global fight against HIV/AIDS. At the same time, however, we must ask ourselves why we, collectively, don't care more about the domestic epidemic. Thousands of young Americans are dying each year of a preventable infection.

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24. I thank M. Chamberland, T. Durham, S. Jones, G. Millett, R. Moseley, and R. Valdiserri for their helpful comments.

別紙様式第 2-1

別紙 3-3

医薬品
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識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2004 年 10 月 21 日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称			研究報告の公表状況	Issue Summary Transmissible Spongiform Encephalopathies Advisory Committee 16th Meeting Oct 14, 2004 Silver Spring, Maryland	公表国 米国	
販売名（企業名）						

研究報告の概要

過去 20 年間, FDA では製造業者に対して血液および血液製剤を介した CJD および vCJD の伝播の理論上のリスク軽減を目的とした勧告を行ってきた。感染した個体を特定できるスクリーニング法が確立されていないため，血液製剤の安全性は CJD および vCJD のリスクがあると考えられる供血者を予め除外し，かつ供血後にその供血者が除外されたという情報が得られた場合には製造を中止するという方法に頼らなければならない。2004 年 10 月 14 日，FDA は伝染性海綿状脳症諮問委員会 (TSEAC) に対し，プリオン遺伝子のコドン 129 でメチオニンがヘテロ接合性である供血者由来の血液および血液製剤に対する追加安全措置の必要性ついて助言を求めた。

FDA の質問は以下のとおり：1) 現在 FDA が勧告している血液および血液製剤を介した CJD および vCJD の伝播リスクを軽減する措置は現在も適切であるか。2) 現在の vCJD に関する科学的データは，血液および血液製剤における潜在リスク軽減措置に関する FDA の見解の正当性を保証するものであるか。3) 現時点で FDA が検討すべき生じ得るあらゆるリスク軽減措置に対する見解。

使用上の注意記載状況・その他参考事項等

Guidance for Industry Revised Preventive Measures to Reduce the Possible Risk of Transmission of CJD and vCJD by Blood and Blood Products. US Dept. Health & Human Services, FDA, CBER. January 2002
www.fda.gov/cber/gdlns/cjdvcjdq&a.htm

報告企業の意見	今後の対応
現時点で, FDA は,「血液および血液製剤を介した CJD および vCJD 伝播の生じ得るリスク軽減予防措置に関する製造業者向けガイドライン (2002 年 1 月発行)」を改定していない。弊社の血漿分画製剤は, 全て米国においてガイドラインを遵守して製造されており，vCJD の伝播の理論上のリスクは極めて低い。	現時点では，弊社の血漿分画製剤の添付文書，採漿方法および製造工程に対して新たな安全対策上の措置を講じる必要は無いと考える。引き続き関連情報の収集に努める。

Issue Summary

Transmissible Spongiform Encephalopathies Advisory Committee

16th Meeting
Oct 14, 2004
Silver Spring, Maryland

Topic #6. Consideration of Current FDA-Recommended Safeguards to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products

Issue

FDA seeks advice from the FDA Transmissible Spongiform Encephalopathies (TSE) Advisory Committee (TSEAC) on whether recent data regarding vCJD warrant consideration of the need for additional safeguards for blood and blood products.

Background

Most attempts to detect infectivity in blood or serum of animals with TSEs failed until 1978, when Elias Manuelidis and colleagues demonstrated the transmissible agent in crude buffy coat preparations of 13 guinea pigs injected with brain material of other guinea pigs with experimental Creutzfeldt-Jakob disease [1], detected throughout most of the incubation period. Assay guinea pigs had long incubation periods (some over a year), suggesting that amounts of infectivity in donor guinea pig blood were probably very small. In 1983, NIH investigators demonstrated that the blood buffy coats of mice infected with a TSE agent derived from a patient with the Gerstmann-Sträussler-Scheinker disease (GSS)—similar to familial CJD—also contained infectivity, detectable from the middle of the incubation period through terminal illness [2]. The finding of small amounts of TSE infectivity in blood was later confirmed in a variety of other animals with TSEs [3-5], including sheep with naturally-acquired scrapie [6] and experimental bovine spongiform encephalopathy (BSE) [7] and chimpanzees injected with brain material from a GSS patient [8]. Although much infectivity was associated with nucleated cells [5, 8-12], plasma contained substantial amounts as well [13].

During the past 20 years the FDA has made recommendations to the blood industry intended to reduce the theoretical risk of transmitting the infectious agents of Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD) by blood and blood products. The history of FDA's policies in this area is summarized in Appendix I. Because no validated screening tests are

available to identify infected units, safety must rely on precautionary deferrals of donors thought to be at increased risk for CJD and vCJD and withdrawal of products when post-donation information reveals that a donor should have been deferred. The Agency, aware of the uncertainties surrounding the magnitude of the risk, the effectiveness of available risk-reducing measures, and the potential for contributing to shortages of life-sustaining blood products, is committed to review at frequent intervals its policies regarding CJD and vCJD. FDA has taken a proactive approach in addressing potential risks from CJD and vCJD consistent with the findings of the Institute of Medicine regarding decision making that took place for HIV and the blood supply [14]. In particular, FDA blood safety policies regarding CJD and vCJD have generally been reviewed publicly with the TSE Advisory Committee, especially when new information suggests that risks should be reevaluated. Since the last meeting of the TSEAC in Feb 2004, the following new information on vCJD has come forward.

Presumptive transmission of vCJD from blood of a second clinically healthy donor. The UK Transfusion Medicine Epidemiology Review (TMER) [15] has identified and enrolled 50 recipients of labile blood components from 16 donors later found to have vCJD in an on-going look-back" study. (In addition, TMER identified nine vCJD donors who contributed plasma to 23 pools used for fractionation into derivatives before 1999.) As of Aug 12, 2004, 13 of 18 surviving recipients of labile blood components had been enrolled in TMER for at least five years; thirty-two recipients had died, two with evidence of vCJD.

On 17 Dec 2003 the UK Department of health announced that one recipient of non-leukoreduced red blood cells had died with vCJD. (The case has been described in detail [16] and was presented at the 15th meeting of TSEAC [17].) In Mar 1996, a clinically healthy young blood donor donated Whole Blood to the UK National Blood Service. Red blood cell concentrate—not leukoreduced—was transfused into an older surgical patient. Three years four months later the donor developed signs of vCJD, confirmed at autopsy. Six and a half years after the transfusion the recipient became progressively demented with other neurological signs and died after 13 months; autopsy revealed vCJD. The recipient was found to be homozygous for methionine at codon 129 of the prion-protein-encoding (*PRNP*) gene, as had been all other persons with vCJD tested. UK authorities estimated the recipient's age-adjusted food-borne risk of vCJD to have been from 1:15,000 to 1:30,000.

In Jul 2004, UK authorities announced that preclinical vCJD had been diagnosed the previous year in a second person in the TMER cohort. (The case has been partially described in the medical literature [18].) The second recipient was

transfused in 1999 with non-leukoreduced red blood cells from a clinically healthy donor who developed signs of vCJD 18 months later, confirmed at death in 2001. Five years after transfusion, the recipient died of a ruptured abdominal aortic aneurysm without signs of neurological disease. Abnormal prion protein typical of vCJD was detected at autopsy in several areas of the spleen and in a cervical lymph node, suggesting that infection was present but had not yet spread to the brain. It seems highly improbable that two cases of vCJD resulting from coincidental food-borne transmission would occur by chance in the small TMER cohort during a short period of time.

Variant CJD in a person heterozygous for methionine at codon 129 of the *PRNP* gene. The second presumptive transfusion-transmitted case of vCJD was in a person heterozygous for methionine at *PRNP* codon 129 [18]—the first time that genotype has been found in any patient with vCJD to be tested. (As noted above, all other vCJD patients tested have been homozygous for methionine at *PRNP* codon 129.) Although the case was preclinical, it seems probable that infection would eventually have progressed to involve the nervous system had the patient not died of an unrelated disease. Homozygosity for methionine or valine at *PRNP* codon 129 is known to be over-represented in persons with iatrogenic and sporadic forms of CJD [19], however heterozygotes have not been completely spared from those diseases. The finding of a transfusion-transmitted vCJD infection in a heterozygote implies that such individuals are unlikely to be absolutely resistant to infection with the BSE agent and that food-borne vCJD cases may be expected in all *PRNP* genotypes, possibly in smaller numbers and with longer incubation periods than for homozygous individuals. In any case, persons heterozygous for methionine/valine at codon 129 of the *PRNP* gene (comprising about half the population in the UK) appear to be susceptible to blood-borne infection with human-adapted BSE agent.

New cases of vCJD per annum peaked in the UK in 1999 and deaths in 2000; only one new case has been reported recently outside the UK [17]. The current total stands at 157 definite or probable cases in UK, three presumably UK-acquired cases dying outside UK (Canada, Ireland, US), seven cases thought to have been acquired in France and one in Italy. The times of residence in and departure from the UK of two cases in North America suggest that the incubation periods of food-borne vCJD may be as short as nine years (Will RG, unpublished observation).

Predictions of vCJD infection rates based on finding of abnormal prion protein in lymphoid tissues of preclinical vCJD.

Shortly after the first descriptions [20], it was noted that lymphoid tissues of a person dying with vCJD (spleen, lymph nodes) contained detectable amounts of abnormal protease-resistant prion protein (PrP^{sc}) [21, 22]. The appendix removed

from an otherwise healthy person who developed signs of vCJD eight months later also contained PrP^{sc} [23], as did another appendix removed two years before onset (a third removed 10 years before onset was negative) [24]; those fortuitous findings suggested that a survey of archived tonsils and appendices might provide some estimate of the minimum number of persons with preclinical vCJD in the UK population. Two such surveys have been reported to date: the first found one positive appendix among 8318 adequate specimens saved from patients 10 to 50 years old between 1995 and 1999, yielding an estimated rate of 120/million (95% CI, 0.5 – 900/million) in that population [24]; the second yielded three positives among 12,674 appendices for an estimated rate of 237/million (95% CI, 49 – 692/million) [25]. All tonsils were negative. It is interesting to note that both tonsils and appendix of the second presumptive transfusion-transmitted case were negative for PrP^{sc}, attributed to the non-food-borne route of infection [18].

Charge to the TSE Advisory Committee

For many years the FDA and other regulatory authorities [26]) have taken very seriously the theoretical possible transmission of all forms of CJD by blood products and has advised blood and plasma establishments to defer donors thought to be at increased risk for CJD.

There have been six general bases for CJD/vCJD-related deferrals [27]:

A. General CJD risk reduction (1) CJD in a donor, (2) history of treatment with pit-hGH or dura mater allograft, and (3) history of CJD in a relative unless confirmed to be other than familial CJD or the donor *PRNP* genotype is found to be normal

B. vCJD risk reduction (1) history of prolonged residence in most BSE countries (defined by USDA list of BSE-related import prohibitions) currently including UK, France or other European countries west of the Former Soviet Union (or residence/employment on a US military base in Europe during periods when beef was procured from UK), (2) history of transfusion in UK in or after 1980, and (3) injection with bovine insulin of UK origin in or after 1980

The FDA CJD/vCJD blood safety policies have been recommended to reduce the risk that a donor might be incubating CJD of any kind while not deferring so many donors as to compromise the supply of blood products. The TSEAC is now asked to consider whether the CJD/vCJD deferral policies currently recommended by FDA to protect the safety of the blood supply remain justified and, if so and considering recent additional information about BSE and vCJD, they are still adequate. If TSEAC considers any current policy inadequate, FDA solicits its advice in suggesting enhancements to existing policies or possible additional

policies that might reduce the risk further without jeopardizing an adequate supply of life-sustaining and health-sustaining blood products.

Questions for the Committee

1. Are the measures currently recommended by FDA to reduce the risk of transmitting CJD and vCJD by blood and blood products still justified?
2. Do the recent scientific data on vCJD warrant consideration by FDA of any additional potentially risk-reducing measures for blood and blood products?
3. If so, please comment on the additional potentially risk-reducing measures that FDA should consider at this time.

Appendix I

History of FDA Policy Making Regarding Risk of Transmitting CJD and vCJD by Transfusion

In Aug 1983, FDA learned that a US blood donor had been diagnosed with CJD; in-date components and plasma derivatives were voluntarily withdrawn. Over the next 12 years there were nine other CJD-related voluntary withdrawals of US blood products. In Nov 1987, FDA, aware that TSE infectivity had been found in animal blood and concerned about a growing number of iatrogenic cases of CJD among people treated with injections of human cadaveric pituitary growth hormone (pit-hGH), issued a memorandum recommending precautionary deferral of blood donors previously treated with pit-hGH—acknowledging a concern about potential transmission of CJD by products from blood of clinically normal at-risk donors [28]. In subsequent years, FDA recommended deferral of other donors thought to be at increased risk for CJD: recipients of dura mater grafts and people with a family history of CJD. In Aug 1995 [29], FDA also recommended—in addition to donor deferrals—precautionary withdrawal of blood, blood components, and plasma derivatives [30] from donors recognized post-donation to have CJD or to be at increased risk for iatrogenic or familial CJD.

After a public announcement in Sept 1998 (and in guidance published in Aug 1999 for immediate implementation with a request for comment and in revised form in Nov 1999 [31]), FDA no longer recommended withdrawal of plasma derivatives from donors at increased risk for most forms of CJD, for several reasons: (1) epidemiological studies failed to find that transfusion with human blood or components or treatment with plasma derivatives was a risk factor for sporadic CJD (summarized most recently at the 15th meeting of the FDA TSE Advisory Committee [32](2) the very large pools of plasma used to prepare derivatives have a high probability of containing a contribution from a donor incubating CJD 33], because CJD has a lifetime risk of one in nine thousand persons with long silent incubation periods, sometimes exceeding 38 years [34], and it is not possible to identify those donors; (3) in experimental spiking studies, the processes used to fractionate plasma have demonstrated a substantial capacity to reduce if not eliminate the infectivity of TSE agents from most final products [35] (though only modestly effective for factor VIII), and (4) withdrawals, while possibly reducing a theoretical risk of transmitting CJD, were thought to contribute to shortages of some plasma derivatives. However, FDA has continued to recommend deferring donors at increased risk for all forms of CJD and to retrieve in-date components when post-donation information revealed that donors either developed CJD or should have been deferred because they had an increased risk for CJD [27].

While no longer recommending withdrawal of plasma derivatives from CJD-at-risk donors, FDA has continued to recommend withdrawals of all plasma derivatives prepared from pools to which any donor later diagnosed with vCJD contributed; fortunately, that has never been necessary in the US, although donors who later became ill with vCJD have contributed to pools used in the manufacture of plasma derivatives in other countries [36]—thus far without evidence of transmission. (Some recipients of plasma derivatives in the UK [15] were recently notified of the results of an assessment exercise to estimate the potential risk [37].)

FDA was more concerned about the theoretical possibility of transmitting vCJD than other forms of CJD via plasma derivatives because vCJD has an age distribution, clinical presentation and course of illness, histopathology and pathogenesis substantially different from those of other forms of CJD [20], and experience with vCJD is much more limited. Hence, the reassuring epidemiological studies that failed to implicate blood products as a risk factor for other forms of CJD might not be predictive for vCJD. For those reasons, FDA concluded that additional precautionary steps were justified to reduce the risk of transmitting vCJD by transfusion of blood components or injection of plasma derivatives. In Aug and Nov 1999 [31] following discussions in TSEAC on Dec 18, 1998 [38]] and using information from a travel survey of blood donors [39, 40], FDA recommended that blood establishments defer blood donors who had spent six months or more in the UK from the start of 1980 (estimated to be a probable earliest date when a significant number of cattle were infected with the BSE agent in the UK) and the end of 1996 (when UK fully implemented a variety of measures to control BSE and prevent human exposure to the BSE agent [41]. That geographically based policy was estimated to reduce exposure to the BSE agent (as total days spent by blood donors in UK) by about 87%, while predicted to defer about 2.2% of US blood donors [40]).

As diagnosed cases of vCJD continued to increase in the UK and former UK residents in other countries and several cases were reported in residents of France (currently seven) and Italy (one), affecting persons who had not visited the UK, FDA, on advice of TSEAC, issued a second Guidance for Industry reducing the recommended time that suitable donors might have spent in the UK to three months and broadening the range of countries considered to pose a risk of exposure to the BSE agent sufficient to justify deferring donors who had spent substantial time there [27]. The acceptable maximum times that otherwise suitable donors might have spent in those other countries were adjusted to reflect risks relative to that in the UK, where the both BSE and vCJD epidemics were the largest: (1) US military bases in Europe were estimated to have about one-third the risk of UK during periods when up to a third of the beef used there was

procured from UK. (The recommended acceptable time spent on affected military bases was six months, to provide an additional margin of safety.) (2) France was estimated to have about 5% of the UK risk, because at least 5% of beef products consumed in France until the early 1990s were thought to have been imported from UK, and, at that time, the number of cases of vCJD in France was about 5% of those in UK, while both countries had roughly similar populations. (3) Other European countries were assigned a nominal BSE risk based on BSE surveillance data from Switzerland, estimated to be about 1.5% of UK risk; although it seemed likely that a number of countries might have actual risks lower than that of Switzerland, the quality of their BSE surveillance was uncertain.

In addition, FDA, concerned about UK blood donors who might be incubating vCJD and a theoretical possibility of further adaptation of the BSE agent to replicate in humans after a transmission by blood, also recommended deferring anyone who had received a blood transfusion in the UK after 1979. No deferrals of donors transfused in France other BSE countries were recommended, however, because the risk of BSE infections of humans was so much lower there. FDA also recommended deferring donors who had been treated with bovine insulin from the UK in or after 1980. (Those and other CJD/vCJD-related policies recommended for donors of Whole Blood are summarized in Table 1 of the Jan 2002 Guidance Document [27].)

The policies recommended for donors of Source Plasma (apheresis plasma) were somewhat different from those for blood (Table 2 [27]). FDA did not recommend deferring donors of Source Plasma for any period of residence in BSE countries other than in the UK and France. (FDA recommended that recovered plasma be treated like all other components so as to discourage the intentional collection of Whole Blood from deferred donors.)

The modified donor deferral policy was estimated to reduce the overall BSE-related risk by 91% (72% of the risk remaining after implementation of the 1999 policies), with a final overall donor loss of 4.6-5.3%; however, considerable geographic variation was expected, including potentially higher donor losses in coastal states and near military bases. (If blood establishments were to be more aggressive in their deferral policies, then both overall donor loss and risk reduction might be higher.) Implementation was recommended in two stages, to be completed by Oct 21, 2002. Because of normal variability in blood donations, probable self deferrals by some donors, encouragement of increased donations by repeat donors, and active recruitment of new donors by blood programs, it has not been possible to evaluate the actual effects of the new policies on the blood supply, except to conclude that obvious shortages have not resulted.

In a joint meeting of the TSEAC and Blood Products Advisory Committee (BPAC) on Jan 17, 2002 [42], FDA solicited advice on whether food chain

controls to prevent human exposure to BSE implemented in the UK since 1996 were sufficient to obviate a need to defer blood and plasma donors based on their subsequent travel or residence there. The reason for review was that a major US blood program had begun to defer blood donors based on time they spent in UK not only after 1980 through 1996 but also after 1996 to the present. The measures thought to be effective in protecting humans from food-borne exposures to BSE agent in the UK were BSE control in ruminants[a] and a number of steps to reduce the likelihood that infectivity present in cattle with unrecognized BSE would enter the food chain[b].

In subsequent meetings of the TSEAC, FDA has acknowledged that three other countries had BSE in native-born cattle: Canada (two cows, one resident in USA at time of diagnosis), Israel (one cow), and Japan (12 cows). The FDA was unable to estimate either the potential risk reduction or the effect on the blood supply of deferring residents in those countries, and the TSEAC did not suggest deferring donors for any period of residence in those countries; therefore the FDA did not recommend deferring donors who lived in or spent time in those countries.

[a] Ruminant feed ban (prohibition of the feeding of ruminant-derived meat-and-bone meal—and most other mammalian proteins—to cattle, sheep and goats), a national BSE surveillance program (including prion protein testing of appropriately selected brain tissues from cattle at increased risk of BSE) compliant with the requirements of the Office International des Epizooties (OIE) to which the USA is signatory, prompt condemnation and destruction of animals with signs of BSE, preventive culling of animals at increased risk, and adequate compensation to owners of condemned cattle in order to encourage compliance

[b] Age-based slaughter schemes (meat from cattle more than 30 months old no longer considered edible in UK), separation of high-risk bovine tissues (specified-risk materials [SRM]) from edible meat and prohibition of slaughter methods that embolize brain tissue into meat, e.g., intracranial air injection and "pithing", application of the same controls to imported and domestic meat products