# Leucodepletion for transmissible spongiform encephalopathies

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**ABSTRACT**

Transmissible spongiform encephalopathies (TSEs) have been recognised around the world for many years. Creutzfeldt-Jakob disease (CJD), one of the human forms of TSE, has been studied widely and thus far has not proved a great threat to human health. The emergence of two new TSEs – bovine spongiform encephalopathy (BSE) in cattle and variant Creutzfeldt-Jakob disease (vCJD) in humans in the UK – has caused great concern. BSE has had an economic impact and vCJD is a threat to human health. It has been shown that these two diseases are caused by the same prion agent and are linked. Research indicates that vCJD behaves differently to CJD and there is strong evidence to suggest that vCJD is present in lymphoid tissues and B lymphocytes, which presents a theoretical risk that it may be transmitted by transfusion of blood and blood products. To minimise/prevent this risk, the UK government has decided that plasma should be sourced from abroad and has instructed the National Blood Service to leucodeplete all blood and blood products, at a cost of £70 million per annum, although it is not known if this will remove this risk.

KEY WORDS: Creutzfeldt-Jakob syndrome. Leucodepletion.

## Introduction

The first possible case of transmission of variant Creutzfeldt-Jakob disease (vCJD) via a blood transfusion was reported in December 2003.[1] The donor gave blood in 1996 when apparently healthy, before universal leucodepletion of blood in the UK, which commenced in November 1997. The donor died in 1999 and the recipient in the autumn of 2003.

Although there is no way of determining whether the recipient acquired the disease through the transfusion or developed vCJD independently, this case has reopened the debate about the safety of the blood supply in the UK. This review considers the evidence that vCJD can be transmitted by contaminated blood products and looks at the role of leucodepletion in preventing transmission.

## Can CJD be transmitted by blood and blood products?

Creutzfeldt-Jakob disease (CJD), first described in 1920, is a fatal and untreatable disease of the central nervous system (CNS) that manifests typically as dementia, spongiform degeneration, astrogliosis and myoclonus.[2] It is a rare, progressive disease and usually causes death within a year.[3] It has a random worldwide distribution and an annual incidence of approximately one case per million population.[4]

The possibility that CJD could be transmitted by donated blood was studied by Esmonde *et al*.,[5] who found that out of 202 definite and probable cases of CJD, 29 patients had donated blood and 21 were recipients of donated blood. Those who received blood showed symptoms similiar to sporadic CJD, and therefore were thought to have sporadic CJD. The symptoms were quite different to those seen in patients who developed CJD due to iatrogenic transmission through human growth hormone treatment. The researchers thought that if CJD was transmitted iatrogenically by blood transfusion, the symptoms would be similar to those seen in patients who had received human growth hormone therapy. Their study concluded that blood transfusion was not a major risk for CJD transmission.

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Klein disagreed with this conclusion and pointed out that four Australians with no history of familial CJD or risk of iatrogenic transmission, but who had received blood transfusions five years before the onset of symptoms, had died from CJD.[6] In a follow-up study, Heye *et al*. traced and followed up recipients of blood from a donor who provided 55 units of blood and who died from CJD. They found no evidence of CJD transmission by blood transfusion, two, 16, 20 and 21 years later.[7]

Creange *et al*. reported that a patient who had a liver transplant and was multi-transfused developed CJD. One of the donors of plasma that was processed to produce albumin and transfused to this patient developed dementia (a symptom of CJD).[8]

So far, transmission of CJD by transfusion has not been seen in haemophiliacs. Such patients are extensive users of blood products and thus are exposed to bloodborne infections. Operskalski and Mosley stated that haemophiliacs have been exposed to fresh blood and blood products since the 1950s and if CJD was transmitted by blood transfusion then there has been ample time for transmission to be observed in this group.[9]

Evatt *et al*. carried out a retrospective study of whether or not CJD was transmitted to haemophilia patients and they found that it was not transmitted by factor concentrates,[10]

which suggests that CJD is not transmitted by blood products.

However, it has been shown that bovine spongiform encephalopathy (BSE) can be transmitted by blood transfusion in sheep. Transfusion of 400 mL whole blood from a sheep during the symptom-free phase of BSE was followed by the development of BSE symptoms in the recipient 610 days after transfusion.[11]

## Variant Creutzfeldt-Jakob disease

A new form of CJD was identified in the UK by Will *et al*., which initially was termed new variant CJD (nvCJD) but subsequently shortened to vCJD.[12] It was thought to be almost certainly linked to BSE, and this was evidenced later in experimental studies using animal models by Collinge *et al*.,[13] Bruce *et al*.[14] and Hill *et al*.[15] Later, Almond and Patterson stated that vCJD 'is human BSE'.[16]

Concerns were raised about transmissible spongiform encephalopathies (TSEs) by the regulating bodies, who were concerned about the risks of iatrogenic transmission of disease by tissue transfer, especially when it was shown that vCJD resembled BSE and was caused by the same prion strain.

## Variant CJD in tissue outside the central nervous system

Hill *et al*. found abnormal prion protein (PrP) in tonsil tissue in a patient who died of vCJD.[17] Hilton *et al*. found abnormal PrP immunoreactivity in an appendix removed eight months (during the incubation period) before the patient died of vCJD.[18] Klein *et al*.[6] found that B lymphocytes played an important role in the neuroinvasion of scrapie and suggested that B cells may carry PrP from lymphoid tissue to nervous tissue.

However, in a later study,[19] it was found that PrP in scrapie ($PrP^{Sc}$) does not need to be present in B cells for neuroinvasion to occur, which suggests that neuroinvasion may be caused by cells whose maturation depends on B cells such as follicular dendritic cells. Mabbot *et al*. also suggested that the immune system is involved in the pathogenesis of TSEs.[20] They stated that tissues outside the central nervous system had a limited role in sporadic CJD and BSE but if the species barrier was crossed, as in the transmission of BSE to sheep, there would be more widespread infectivity.

In a study carried out by Hill *et al*.[21] it was found that all lymphoreticular tissues (tonsil, spleen and lymph nodes) taken from patients who had died of vCJD had $PrP^{Sc}$. They did not find $PrP^{Sc}$ in these tissues in patients who had died of other prion diseases including sporadic CJD. They stated that the distribution of the agent thought to cause vCJD in human tissues differs from that of sporadic CJD. They demonstrated that the abnormally conformed PrP is detectable in peripheral lymphoid tissue in vCJD patients, which leads to the possibility that it could be present in lymphoid cells in blood.

Based on these findings, the risks of iatrogenic transmission of the disease could be different from those associated with sporadic CJD. There might be a greater risk of accidental transmission of vCJD, which raises the possibility that it could be transmitted by the transfusion of blood and blood products.

Relatively reassuring epidemiological evidence from the study by Esmonde *et al*.[5] of sporadic CJD may not be relevant to vCJD. Therefore, theoretically, vCJD may be transmitted through blood and blood products, thus posing a threat to the safety of the blood supply.

## Possible reasons for non-transmission by transfusion

There are a number of reasons why the transmission of CJD and vCJD by transfusion has not been confirmed to date. These include the possibility that the disease is not transmitted by blood and blood products in clinical practice; low prevalence of the disease in the blood donor population; absence or low concentration of the infectious agent in plasma for fractionation; removal of the infectious agent by the processes used to manufacture human plasma products; and, the disease's long incubation period in recipients.

There have been two reports of CJD transmission by transfusion,[8,22] but these cases have not been well documented or supported by convincing evidence. Time will tell if human blood is a route for transmission, as it is believed that peripheral inoculation involves a long incubation period. Unless a suitable serological assay is developed, the prevalence of these diseases in the donor population will remain unknown; however, prevalence in the donor population should reflect that in the general population. This notwithstanding, there are some indications that the infectious agent may be reduced by manufacturing processes used in the production of some blood products.[23]

## Blood donations from those who died as a result of CJD and vCJD

Ten to 15 per cent of all cases of sporadic CJD were blood donors,[5] as were 20.8% of vCJD cases.[24] Therefore, a significant number of recipients have received both labile products and blood components from plasma pools. Evidence of CJD or vCJD transmission through study of the recipients of these donations will take years to accumulate because of the potentially long incubation period involved.

Foster[23] carried out an assessment of the risks of CJD transmission to patients treated with plasma products derived from donors in the UK. There are a number of blood products prepared for medical use from pooled donations of human plasma. These include normal and specific immunoglobulins, coagulation factor concentrates and solutions of albumin. Foster attempted to determine the extent to which the procedures used for plasma fractionation were capable of eliminating the vCJD agent from plasma products. If pooled plasma was infected with vCJD, he concluded that the quantity of abnormal PrP present would be substantially reduced during the preparation of each of the plasma products. However, he added that it is not known whether or not the processes were capable of removing all infectivity, as this depended on the amount of agent needed to cause infection.

Following experimental transmission of CJD using human blood, Brown[25] thought that there could be a low level of

infectivity in human plasma concentrates and therefore a small potential risk of disease transmission.

## Sourcing plasma outside the UK

Ludlam[26] expressed concern on behalf of the executive committee of the United Kingdom Haemophilia Centre Directors' Organisation (UKHCDO) on the safety of plasma products made from plasma donated in the UK. The Committee for Proprietary Medicinal Products issued a directive to withdraw two batches of factor VIII because they were produced from plasma comprising donations from individuals who subsequently developed vCJD. If increasing numbers of UK donors prove to be infected with vCJD in the future then more batches of products would have to be recalled, causing both logistical problems and a danger to recipients.

Regular users of blood products (e.g., haemophiliacs) are exposed to person-to-person transmission of bloodborne infection.[27] Prior to 1990 (when testing began), haemophiliacs were exposed to hepatitis C and human immunodeficiency virus (HIV). Therefore, great caution should be exercised in order to prevent the introduction of another bloodborne infection.

Owing to the uncertainty that surrounds vCJD transmission by blood and blood products, the UK government decided, as a precautionary measure, to ban the fractionation of plasma donated in UK and replaced it with plasma sourced from abroad. However, according to Foster,[28] this has not been without its problems. The initial decision by the US Food and Drug Administration (FDA) to recall batches of plasma from donors found subsequently to be at risk, as well as those who developed CJD, led to shortages of plasma. Therefore, the FDA revised its decision to recall products from donors subsequently diagnosed with vCJD, which is in line with European plasma products recall policy.

## Testing donated blood

Final confirmation of a diagnosis of CJD and vCJD is made on neuropathological examination of tissue removed during post-mortem examination, while suspected cases can be diagnosed on neurological examination. However, during the incubation period and before the clinical onset of disease, it is now possible to diagnose cases by tonsil biopsy and using material taken from the appendix.[17,18,20]

To date, there is no serological assay available to identify infected individuals during the preclinical phases of the disease. Blood donors, therefore, cannot be tested for abnormal PrP at the time of donation. The difficulty in developing a diagnostic test is due to the fact that PrP is devoid of nucleic acid and therefore diagnostic techniques and molecular biological approaches used in the development of other assays are ineffective and cannot be applied in the detection of the agent (which may not, of course, be present in blood).

According to Turner,[29] TSEs do not produce a familiar immune response (e.g., production of antibodies), presumably because the immune system is tolerant of host PrP, the abnormal forms of which cause these diseases. MacGregor *et al*.[30] identified the distribution of the normal PrP isoform in human blood. In their study they used a time-resolved dissociation-enhanced fluoroimmunoassay and found that 68.5% of PrP was in plasma, 26.5% in the platelet fraction and the remainder in leucocytes and red cells. They suggested that the use of an assay to identify the distribution of PrP could lead to the development of a diagnostic serological assay to identify abnormal PrP in blood and plasma.

## Prevention of vCJD transmission via transfusion

In the absence of a donor screening serological assay, a number of strategies and measures have been assessed and implemented to prevent the theoretical risk of vCJD transmission via the transfusion of blood and blood products. These include sourcing plasma for fractionation from outside the UK, optimising the use of blood and blood products, identification and exclusion of blood donors at higher risk of developing the disease, and the removal of leucocytes. The last measure is important because leucocytes are thought to be the likely means by which transmission could occur.

## Donor selection and health questionnaire

In order to protect recipients and to prevent/minimise the transmission of transfusion- transmitted infections including hepatitis B, hepatitis C, syphilis, HIV, CJD and vCJD in blood and blood products, the National Blood Services has introduced policies that cover the screening, deferral and withdrawal of donors. These are changed as new transfusion-transmitted infections emerge and as more information becomes available on existing ones.

Donors are required to complete a health check questionnaire,[31] the aim of which is to identify those who may have been exposed to infections that can be transmitted in blood and blood products, and to ensure that the donors are fit and healthy. An assessment is then made on the donor's suitability to donate blood, based on UKBTS/NIBSC guidelines.[32]

If a donor is attending for the first time or has not attended for two years, a healthcare professional asks the questions on the questionnaire in a confidential interview; however, if the donor has attended within the previous two years then they are allowed to complete the questionnaire themselves. The NBS relies on donors to answer the questions truthfully; however, they have to sign a declaration to say that their blood donation is fit for use.

## Exclusion of donors considered to be at higher risk of CJD and vCJD

It has been shown that iatrogenic transmission of CJD is possible[33] and, although there are no well-documented cases of transmission by transfusion, many countries (including the UK) have adopted policies that exclude individuals considered to be at higher risk of developing CJD from being blood donors. In addition to this, and as a precautionary measure against the transmission of vCJD, US and Canadian

authorities have implemented the permanent exclusion of donors who have spent six or more cumulative months in Britain during the period between 1 January 1980 and 31 December 1996.[34,35]

Individuals considered to be at higher risk are those with CJD or vCJD, those with a family history of CJD, those who have received human pituitary gland extracts (e.g., growth hormones and gonadotrophin), and individuals who have had operations for tumours or cysts on the spine. So far, these are the only known risk factors that can be applied from a transfusion-transmission point of view for these prion diseases, and are the only criteria where exclusion can be made.

Thus, individuals with CJD, vCJD or another prion-associated disease, and those identified as being at high risk of developing CJD and prion-associated disorders, such as recipients of dura mater grafts, corneal or sclera grafts, human pituitary-derived extract recipients and individuals who have a familial risk of prion-associated diseases are permanently excluded from donating blood.[32] However, donors treated exclusively with recombinant growth hormone are accepted as donors (this has been the case in the UK since 1987).

Some of these exclusions for CJD have been NBS policy for quite some time. For instance, recipients of human pituitary extracts have been excluded from donating blood since 1989,[36] as they will remain at risk for the next 35 years or so.[33]

If a donor chooses not to be truthful in completing the questionnaire, it would be impossible to discover if they were incubating a prion disease because currently there is no donor screening assay to detect it. If a donor conceals exposure to HIV or hepatitis, however, antibodies to these viruses are tested for as a matter of standard practice. If positive for such antibodies then the donation is discarded.

As the route of TSE infection from cattle to humans now seems to have been removed, blood transfusion may be the only way that a future epidemic of vCJD could occur and persist in the population. Thus, it seems logical to exclude anyone who has received blood and/or blood product transfusions from donating until such time as an assay is available. Implementation of such a strategy, however, would have some difficulties.

First, exclusion of transfusion recipients from donating may be seen as an admission that vCJD can be transmitted by transfusion. It may cause panic, worry and anxiety among some recipients, although others may fully understand and accept why they are being excluded. Anxiety could increase because there is no serological assay available to establish whether someone is infected or not.

Another difficulty would be the impact of losing a number of donors, although this could be offset by a decrease in the demand for blood by optimising its use by clinicians. Another issue that needs to be addressed is whether or not recipients of leucodepleted products would be excluded.

## Leucodepletion

Leucodepletion is the removal/reduction of leucocytes from donated blood and blood products. The specification for leucodepletion, as defined in the UKBTS/NIBSC guidelines,[32] is that 99% of products tested by statistical process monitoring methodology should contain fewer than $5 \times 10^6$ leucocytes per unit (within 95% confidence limits).

For a number of years prior to the introduction of universal leucodepletion, the NBS collected leucodepleted platelets by apheresis using Cobe Spectra cell separator machines at various centres around the UK. In addition to which, it produced a quantity of leucodepleted blood products from donated whole blood for use in intrauterine transfusions, potential bone marrow transplant patients, and those experiencing febrile transfusion reactions.[37]

## Established benefits of leucodepletion

Adverse effects of transfusion such as platelet refractoriness, human leucocyte antigen (HLA) alloimmunisation, febrile reactions and graft versus host disease are thought to be caused by the leucocytes present in transfused blood products.[37] Standard techniques used in producing blood products leave $2–3 \times 10^9$ leucocytes per red cell unit and $10^7–10^8$ leucocytes per unit of platelets. The benefits of transfusing leucodepleted blood products containing fewer than $5 \times 10^6$ cells per unit to recipients suffering from certain conditions have been reported in some studies.

Jensen *et al*.[38] demonstrated that leucodepleted blood products can reduce the incidence of post-operative wound infection and intra-abdominal abscess in colorectal surgery. They suggested that leucocytes present in blood products have an immunosuppressive effect on host defences, resulting in the development of post-operative infectious complications, and recommended the use of leucodepleted blood products in this type of surgery. However, a study carried out by Goodnough *et al*.[39] concluded that the filtering of random pooled platelets at the bedside did not reduce the prevalence of platelet-associated reactions and therefore bedside leucodepletion provided no benefit.

Bowden *et al*.[40] showed that leucodepletion by filtration is as effective as using cytomegalovirus (CMV)-seronegative products in preventing transfusion-associated CMV infection in bone marrow transplant patients. They suggested that other groups of immunocompromised patients (e.g., newborn infants and solid organ transplant patients) may be protected from CMV infection by products leucodepleted by filtration. This study was carried out at patients' bedsides and thus the quality of the product could not be guaranteed. They suggested that the quality of the product could be improved and guaranteed if leucodepletion was done in blood service centres.

Demand for CMV-seronegative blood products has increased steadily, in parallel with the number of immunocompromised patients. However, the donor population has a high prevalence (48%) of seropositivity,[41] and the supply of CMV-seronegative blood products may become a problem if this trend continues. The Council of Europe has approved the use of leucodepleted blood products as a safe alternative where CMV-seronegative blood products are unavailable.[42]

Bedside filtration of blood products is expensive, may not prove effective, and its quality cannot be guaranteed.[37,39,40] Thus, the introduction of universal leucodepletion would render bedside leucodepletion unnecessary, and replace it with a product of assured quality that all recipients could benefit from.

## Universal leucodepletion of blood and blood products

A number of researchers[17-19] have found that vCJD is present in lymphoid tissue and cells of the immune system, particularly B lymphocytes. Thus, if vCJD can be transmitted by blood transfusion, it is likely that lymphoid cells and especially B lymphocytes will be involved.

Following government instruction, preparation for the leucodepletion of all blood and blood products by the National Blood Authority (NBA) commenced in November 1997. The government took advice from the Spongiform Encephalopathy Advisory Committee (SEAC) and the Advisory Committee on the Microbiological Safety of Blood and Tissues (MSBT) and commissioned Comer and Spouge[29] to undertake an independent risk assessment of human-to-human transmission of vCJD. If this risk assessment indicated that leucodepletion was necessary then the NBA was prepared to implement leucodepletion as soon as practicable.

In carrying out the risk assessment, the assessors made the assumption that infectivity is present in peripheral blood during the incubation period and, based on the number of individuals who may develop the disease, they concluded that a theoretical risk of vCJD transmission existed. The government accepted the findings and decided, on the advice of SEAC, that all blood and blood products should be leucodepleted[40] as a precautionary measure to safeguard transfusion recipients from vCJD.

The committee could not be certain that the infectious agent was present in blood but, if present, SEAC thought that it would be in the lymphocytes and that leucodepletion may reduce the risk. However, according to SEAC, the precise impact of leucodepletion on reducing the theoretical risk of transfusion transmission would be difficult to assess because it would be years before results were available.

With the introduction of universal leucodepletion, the NBS has had to deal with changes to the collection and processing of whole blood, and suitable filters have had to be evaluated and validated. Williamson *et al*.[43] reported four studies which showed that leucodepletion of whole blood prior to processing into its components results in red cells and plasma of acceptable quality. In addition, they evaluated an in-line whole-blood filter (WBF-1 Pall Medsep, Covina, USA) and found that it provided a convenient method for the production of leucocyte-depleted SAG-M red cell concentrates and plasma.

Changes have been made to the blood collection bags by manufacturers, and staff have been trained in new processes and procedures, which have had to be validated and approved as effective. However, according to Robinson,[34] leucodepletion of all blood and blood products in the UK was achieved by 31 October 1999, and the NBA estimates the cost of leucodepletion to be approximately £70 million per annum.[44]

## Will leucodepletion prevent the theoretical risk of vCJD transmission?

Presently, it remains uncertain whether blood or any of its components (platelets, plasma or leucocytes) can transmit vCJD via the transfusion process; what level of infectivity would need to be transmitted; and, if infectivity is confined to leucocytes, would reduction in leucocyte numbers in blood products to fewer than $5 \times 10^6$ per unit be sufficient to prevent transmission.

An upper limit of $5 \times 10^6$ cells per unit has been found to prevent HLA alloimmunistion, platelet refractoriness, febrile reactions and graft versus host disease, but it is unknown if this is sufficient to prevent transmission of vCJD. Also unclear is whether or not it is necessary to remove particular types of leucocyte, and, if so, are they being removed by current filtration methods. Murphy[43] thought that filtration might increase the risk of transmission because leucocyte membrane fragments carrying the abnormal or free PrP protein could pass through the filter.

As the effectiveness of leucodepletion in removing the potential for transmission of vCJD has yet to be proved, is spending £70 million per annum to implement leucodepletion cost effective? This is difficult to answer, but leucodepletion does offer other benefits. Reducing post-operative infections may cut the length of a patient's stay in hospital, thereby making a cost saving. Routine CMV testing may no longer be necessary because the use of leucodepleted products has been shown to be just as effective as CMV-seronegative products. Are these good enough reasons to implement universal leucodepletion? Based on what is known, it is in everyone's interest, and particularly the recipients of blood and blood products, that leucodepletion be implemented.

The way that the BSE crisis was handled has met with much criticism. The SBO ban that excluded highly infectious parts of cattle from entering the human food chain was implemented in 1989, following the first case of BSE, and was strengthened in 1996 by further legislation. During this time the government offered reassurance that British beef was safe to eat – a fact later proven to have been misleading. Perhaps it was thought that BSE would act in the same manner as scrapie and not affect humans. From a political point of view, the government must be seen to act on the recommendation that leucodepletion be introduced, whatever the cost, or it could lose public confidence on this issue.

## In summary

It remains unclear whether or not vCJD can be transmitted from donor to recipient via the transfusion process, and the true scale of the epidemic in the UK is not known. Nor is it clear whether leucodepletion was necessary, sufficient or effective in preventing vCJD transmission.[45] To date, there have been a total of 139 deaths from vCJD in the UK, but annual figures appear to be falling from their peak in 2000.[46] Currently, any risks from vCJD cannot be quantified but failure to act on what is known about the disease may not be acceptable.

If leucodepletion does remove the risk of vCJD transmission then the cost of its implementation could be justified on this alone. However, if leucodepletion does not remove the risk (or there is no risk to remove) then the other benefits of leucodepletion, such as the reduction in post-operative infections, the prevention of transfusion-associated CMV infection, HLA alloimmunisation and graft versus host disease, more than justify the cost of its implementation.

However, some of the cost can be offset against savings from the discontinuation of bedside leucodepletion, the reduction in in-patient stay due to the reduction in post-operative infection, less CMV testing, and a reduction in the costs associated with collecting donated blood (optimising blood transfusion has led to a decrease in demand for blood and thus a decrease in the amount of donated blood that needs to be collected).[47]

Further research is needed to develop an effective serological assay that could be used to screen donors and exclude those infected with PrP from donating blood.[48] Such an assay could also be used to diagnose disease in the general and patient populations. Furthermore, there is a need to develop techniques and procedures to inactivate PrPs in blood and blood products so that plasma can be sourced from UK donors once again.

If an effective serological assay were developed and implemented, and if it indicated that large numbers in both the patient and the donor populations are positive for PrPs, the exclusion of positive donors may not be necessary. This, however, is an ethical issue and needs further discussion and exploration. There are several reasons why such donors should not be excluded from donating if they are asymptomatic and otherwise healthy and well. If large numbers of donors are found to be positive then large numbers of the patient population may also be positive. Excluding these donors may cause a shortage in the blood supply; however, allowing asymptomatic positive donors to donate specifically for PrP-positive patients might minimise any shortage.

Finally, there is the issue of whether or not donors would want to be tested for vCJD when a serological assay becomes available. Some might prefer not to know the outcome of such a test and may stop giving blood. This could lead to shortages if a significant number of donors took this step, and measures would have to be taken to resolve this issue. □

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