Should blood donors be tested for Variant Creutzfeldt-Jakob disease?

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Health Council of the Netherlands

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Presentation report

Madam State Secretary,

Since it has become clear that variant Creutzfeldt-Jakob disease is transmissible via blood transfusions, major efforts have been made to develop a test that allows for the detection of abnormal prion proteins in the blood. As soon as such a test is available, the question will arise as to whether it should be introduced at the blood banks. One obvious reason for considering the introduction is the protection of people who have to undergo a blood transfusion. But testing for vCJD may have far-reaching negative implications for the donor and also for blood supplies in general, especially if an initial test were to generate many false-positive results in addition to true-positives. This dilemma requires timely consideration, both by government and by the Sanquin Blood Supply Foundation.

In the publication that I am presenting to you today the Health Council has outlined the most important arguments for and against. The text has been drafted under the joint responsibility of the Standing Committee on Medical Ethics and Health Law and the Blood Working Group. An earlier version has been discussed within the Standing Committees on Medicine and Immunology & Infectious Diseases and was also submitted to Sanquin.

It concerns a 'horizon-scanning report' from the Centre for Ethics and Health (CEG). The aim of these reports is to draw attention in a timely fashion to

scientific developments that are of public health importance from an ethical perspective. That is clearly the case here.

I would draw your attention to the 'Agenda' formulated in chapter 6, which highlight those aspects that are particularly deserving of further consideration and decision-making. I can imagine that it may be desirable at some juncture for the Health Council to issue further advice about particular aspects. The Blood Working Group will, in any event, continue to monitor the developments in this field closely.

Yours sincerely,

(signed)
Prof. dr. J.A. Knottnerus
President

Contents

Summary

Variant Creutzfeldt-Jakob disease (vCJD) is one of the prion diseases (disorders that arise from an irreversible mutation in the prion protein). The BSE epidemic in the United Kingdom is generally acknowledged to have been the cause of this disorder. Variant CJD displays a different clinical and pathological picture from the classic form of Creutzfeldt-Jakob disease (CJD) in that young people can also contract the disease and in many patients vCJD initially manifests itself in behavioural changes, which result in a visit to a psychiatrist. The patients usually die after a period of just over one year. A decade after it was first reported, vCJD remains a progressive and invariably fatal disease.

The ability to detect abnormal prion protein in lymphoid tissue from vCJD patients by means of the so-called Western Blot test paves the way for laboratory testing. The British government has commissioned retrospective research on tonsil and appendix tissues removed during operations. Extrapolation of the results of this research suggests that abnormal prion proteins are detectable in 237 per million inhabitants of the United Kingdom. No data of this kind are available for the Netherlands. The prevalence here is presumed to be lower than in the United Kingdom, but how much lower is not known.

It is highly probable that transmission of vCJD via blood transfusions has occurred. In the United Kingdom, two recipients of cellular blood products (derived from a donor who was subsequently to develop vCJD) have died from vCJD. The chances of these deaths being unrelated to the receipt of the blood transfusions are extremely slim. In a third recipient, who died of a different cause, abnormal prion proteins were detected in spleen and lymph nodes.

Transmission via blood transfusion has led to calls for a rapid, non-invasive test based on the detection of abnormal prion protein in the blood (the previously mentioned Western Blot test does not have these characteristics). Various companies and university groups are busy developing just such a test and rapid advances have been made. It is expected that a test suitable for use in a blood bank will be on the market within a few years. The test characteristics are not known at present, nor is it clear what the costs of introducing such a test will be. Nevertheless, there will probably be great pressure to introduce this test in the United Kingdom. The case for and against testing will probably also be debated in France and Ireland in the relatively near future. This issue will also need to be considered in the Netherlands, partly because introduction elsewhere may act as a precedent.

The framework for decision-making in this area will be defined by government's constitutional and internationally enshrined responsibility for the availability and safety of blood supplies. That responsibility is fleshed out in the Blood Supply Act (Wibv). Implementation has been entrusted to the Sanquin Blood Supply Foundation. The basic premise of the Blood Supply Act is that the supply of blood in the Netherlands "must satisfy stringent safety and quality requirements". The government has repeatedly emphasised that this does not mean maximum safety, but optimum safety. After all, maximum safety would mean ruling out every possible risk, regardless of the relationship between the health benefit that stands to be achieved and the costs and other disadvantages associated with this measure. The limited financial resources available within the healthcare system are not the only reason why such an approach cannot be justified.

Tests are performed on donors and their blood in order to protect the recipients against blood-borne diseases. In the case of serious, untreatable disorders, however, a dilemma arises. After all, the corollary is then that a positive (i.e. abnormal) test result may have extremely far-reaching consequences for the donor. It is very emotionally distressing to discover that you have an increased risk of developing a serious disease which can neither be treated nor prevented. This information may also have negative implications for the person concerned as far as work and insurability are concerned, or otherwise may lead to exclusion and stigmatisation. This makes testing for such disorders, and therefore also for vCJD, both morally and legally problematic.

Furthermore, if the introduction of a test for vCJD were to result in large numbers of donors being deterred from continuing to give blood, this could jeopardise the maintenance of adequate blood supplies. For various reasons, it is unacceptable – also from a legal standpoint – to test the donor and then not inform him/her of the result. The question therefore arises as to whether it is sensible to test for vCJD if the price to be paid for securing this greater safety would be that insufficient blood is available to meet the needs of patients.

A further significant problem in this connection is the large number of false-positive results that can be anticipated. If prevalence is low, this problem cannot be avoided even by using a relatively specific test. Also to be taken into consideration is the fact that an initial test is probably less discriminatory and that a confirmatory test may not yet be available at first. Besides causing unnecessary anxiety, false-positive results also result in further exclusion of donors. False-negative results, which probably occur far less often, engender unwarranted reassurance in the donor and a lack of certainty in the recipient.

The decision-making over the possible introduction of a test for vCJD will in any case take place under conditions of great scientific uncertainty. Relevant considerations are the question of whether the greater safety for recipients offsets the disadvantages of testing for the donors, the extent to which such a test will, in fact, undermine donor willingness, and the cost-effectiveness of testing for vCJD. Further research – both into attitudes among donors and into the prevalence of abnormal prion proteins in the Netherlands – can only go so far in helping to reduce the continuing uncertainties. The question of what we are to understand by 'optimum' blood safety in

this context is still unresolved. This issue is further complicated by the fact that public perception of risk is also shaped by all manner of affective (and consequently less 'rational') factors.

Under the Blood Supply Act, the government can decide that blood donors must be tested for vCJD. However, the Sanquin Blood Supply Foundation – the privatised blood supplier – also bears a responsibility of its own. Clearly, concerted policy development is desirable, also because of such aspects as financing and liability.

If it is decided to introduce testing, additional measures will be required in order to minimise undesirable consequences for donors and others. First of all, the donor must be adequately informed about the test for vCJD and its possible implications. Then donors with a positive test result must be offered counselling services. Donors who test positive must be assured of adequate care and protected against forms of stigmatisation and social exclusion. We must assess whether (and under what circumstances) it is desirable to trace and inform the recipients of earlier transfusions with blood from donors who have been found to test positive. For the protection of third parties, steps must be taken to prevent further transmission of abnormal prion proteins in the course of delivering medical care to donors who test positive.

If the outcome of the decision-making is that a test for vCJD is not introduced in the Netherlands (for the time being, at least) because such a measure would not be consistent with a policy that is geared to optimum safety, or because the negative consequences of its introduction outweigh the positives, then the emphasis will shift from the consequences for the donor to the implications for the recipient. In the event of adverse health effects that could have been avoided by testing for vCJD, Sanquin (and possibly also the government) may be held liable. The precise legal implications in this scenario require closer consideration. From a moral perspective, consideration also needs to be given to the possibility of compensating people who contract vCJD as a result of the decision not to test donors.

It is also possible that calls may be made for the introduction of a test for vCJD in other areas of medicine, in order to protect patients and care providers against the risk of transmission. Two such areas are surgery (especially neurosurgery) and transplantation medicine. Here too, timely consideration of the pros and cons of a test for vCJD is desirable. This is primarily a matter for the relevant professional groups and patients' organisations to consider.

1 Introduction

1.1 Background and aim of this horizon-scanning report

Ever since evidence emerged that vCJD (variant Creutzfeldt-Jakob disease) can be transmitted via blood transfusions, there has been feverish activity in various locations with a view to developing a presymptomatic test that can be used in blood banks. The tests that are currently under development are based on the detection of abnormal prion proteins in the blood. The theory is that by excluding people with abnormal prion proteins from donating, it might be possible to protect recipients of blood and blood products against the risk of transmission.

However, this hypothesis is not without its problems from a moral and social standpoint. After all, one would be testing for an extremely serious and as yet untreatable disease. Is it acceptable to ask blood donors to undergo such a test? And will people still want to give blood if they know what a positive (abnormal) test result would mean for them?

Can one introduce such a test if there is still a major risk of false-positive results? Once such a test is available, there will possibly also be calls for its use in other spheres of medicine. Finally, it is conceivable that this will be requested by individuals who suspect that they may be infected and want to be certain. In each of these scenarios, the possibility of testing for a serious, untreatable disorder such as vCJD raises normative questions.

The aim of this horizon-scanning report is to address those questions in a timely fashion, so that policymakers and practitioners can prepare themselves to provide answers, no matter how problematic this might prove to be.

1.2 Structure

The structure of this report is as follows. First we shall spend two chapters outlining the salient facts. Chapter 2 discusses the nature and the seriousness of vCJD and examines the uncertainties regarding the anticipated number of patients. Chapter 3 looks at vCJD and blood banks, examining the question of transmissibility via blood or blood products and the major outstanding scientific problems surrounding the development of a practical test. This is followed in chapter 4 by a discussion of the normative questions raised by this development from both the ethical and the legal standpoint. Chapter 5 examines the implications of a decision for or against vCJD tes-

ting, as well as the importance of giving timely consideration to the question of whether such a test is also desirable in other areas of medicine. Finally, in chapter 6, we formulate the key points that policymakers need to consider.

1.3 Responsibilities

This Health Council horizon-scanning report forms part of the *Signalering Ethiek en Gezondheid 2006* [Monitoring Report on Ethics and Health]. It has been produced under the responsibility of the Standing Committee on Medical Ethics and Health Law and the Blood Working Group by the two scientific secretaries, dr. W.J. Dondorp and dr. K. Groeneveld. The membership of the standing committee and the working group is given in Appendix 1. Comments have been received on parts of an earlier draft from external experts (see Appendix 1) and from the Board of Directors of the Sanquin Blood Supply Foundation.

2 Variant Creutzfeldt-Jakob disease

This chapter contains brief information about the nature of the disease and our as yet incomplete understanding of its prevalence. A more detailed discussion can be found in earlier Health Council advisory reports.[1,2]

2.1 Variant CJD is a serious and fatal disease

A report was published in 1996 about the first ten vCJD patients in the United Kingdom.[3] Variant CJD is one of the prion diseases, which arise from an irreversible change in the structure of the normal cellular prion protein (PrP^{C}), which is expressed in a number of cell types. The precise function of this protein is not known.[4] The conversion of PrP^{C} results in abnormal prion protein, for which two abbreviations are used: PrP^{Sc} (Sc = scrapie, a prion disease in sheep) and PrP^{RES} (RES = resistant, on account of the insensitivity of the abnormal prion protein to enzymatic degradation). Abnormal prion protein is detectable in the brain of vCJD patients, but also in lymphoid tissue (e.g. the tonsil).

The first publication about vCJD identified the BSE epidemic in the United Kingdom as the possible cause of this disease[3] and this idea has meanwhile come to be widely accepted. The consumption of infected beef also emerges in epidemiological research as the principal risk factor for vCJD.[5] Although it is particularly difficult, with such a general source of infection, to draw a firm conclusion about the incubation period of the disease, around ten years is mentioned in several publications.[6,7]

Variant CJD displays a different clinical and pathological picture from the classic form of Creutzfeldt-Jakob (CJD). A key difference is that young people can also contract this form of the disease. The median age for the appearance of the first clinical symptoms is 26 years (range: 12 to 74 years).[8] In many patients the disease initially manifests itself in behavioural changes, which result in a visit to a psychiatrist. Later, these are followed by increasing involuntary movements and serious cognitive impairments. Patients die after a period of a little over one year (median: 14 months; range six to 40 months).[8] In earlier advisory reports, the Health Council characterised vCJD as a progressive and invariably fatal disease.[1,2] This still holds true today, ten years after the disorder was first described.

On 1 December 2006 there were 162 vCJD patients in the United Kingdom and 21 in France.[9] In the Netherlands, vCJD has been diagnosed in two patients in the past two years.[10,11] Isolated cases of vCJD have also been reported in various other European countries and in Japan. There was a peak in the number of newly diagnosed patients in the United Kingdom in 1999 and this has declined in recent years as a result of measures relating to animal feed and slaughter practices. In France, on the other hand, the number of new patients has continued to rise steadily in recent years.

There is no evidence that prion diseases are transmitted from mother to child[12,13] – or at least those children whose mothers either already had vCJD at the time of their birth or developed the disease later have not so far contracted vCJD.[12] However, in view of the very small number of children concerned and the long incubation period of vCJD it is impossible to be absolutely certain on this point.

2.2 Estimates of prevalence vary

The first estimate of the total number of possible patients in the UK emerged within just a short time of the publication describing the clinical picture.[14] Owing to the shortage of data, the total numbers of anticipated patients in these and subsequent estimates ranged from less than a hundred to many thousands.[14,15] The British estimates have always been adjusted downwards on the basis of the actual developments.[13]

The ability to detect abnormal prion protein in lymphoid tissue by means of the Western Blot test paves the way for laboratory testing. The British government has had retrospective research performed on tonsil and appendix tissues removed during operations. Abnormal prion protein was discovered in three out of 12,674 specimens tested.[16,17] Extrapolation of this data suggests that abnormal prion proteins are detectable in 237 per million UK inhabitants. Whether these carriers of abnormal proteins will subsequently develop vCJD is not known.

No abnormal prion proteins were detected during an initial prospective study performed with 2,000 specimens from tonsils removed during operations.[18] The authors state that this result cannot provide reassurance, however, because of the relatively limited scope of the study.[18] A larger-scale prospective study is currently under way.[19]

No data are available with regard to the prevalence of vCJD in the Netherlands. Given the imports of British beef in the 1980s, the Dutch population probably has been exposed to the BSE agent.[2] However, it is not known how much of that meat was actually consumed in the Netherlands and how much was shipped on to other countries.

2.3 New findings arouse fresh concerns

The prion protein gene displays variation in codons (parts of genes that code for amino acids). For codon 129 of the gene, two variants have been described which code for the amino acids methionine or valine.[20] These two variants give rise to three genotypes: homozygous for methionine (MM), homozygous for valine (VV) and heterozygous (MV). Around 40 per cent of humans are methionine-homozygous, ten per cent are valine-homozygous and 50 per cent are heterozygous.[4,20]

All vCJD patients tested to date are methionine-homozygous.[21,22] Research into the properties of the prion protein suggests that the conversion from the normal to the abnormal form occurs more easily in methionine-homozygotes than in heterozygotes or valine-homozygotes.[23,24] However, abnormal prion proteins have also been detected in tissue from a total of three individuals belonging to these two other genetic subgroups. During laboratory testing for abnormal prion protein in lymphoid tissue (discussed in section 2.2), it was possible to perform genetic analysis on two of the three positive samples. Both were found to be derived from individuals who were homozygous for valine.[25] Finally, abnormal prion proteins were detected post mortem in spleen and lymph nodes from the recipient of a cellular blood product from a patient who later developed vCJD (see section 3.1).[26] This recipient, who had died from a cause other than vCJD, was heterozygous.[26]

These data have raised a number of new questions. For example, it is not clear at present whether heterozygotes and valine-homozygotes remain carriers of the abnormal prion proteins or whether they go on to develop vCJD – possibly with a far longer incubation period or a different clinical manifestation. This uncertainty has undermined the published estimates concerning the anticipated total numbers of patients. Those estimates assumed that only methionine-homozygotes would be able to contract the disease and they may therefore be over-cautious. It is also possible that carriers – whether or not they become clinically ill – may, in fact, be capable of transmitting the abnormal prion proteins via blood transfusions to (methionine-homozygous) recipients, who will then go on to develop vCJD.[25]

Evidence to suggest that prion disease may occur in the other genetic subgroups has been obtained from research in patients with kuru and from animal studies. Kuru is a prion disease that occurs in tribespeople from Papua New Guinea as a result of the now-abandoned ritual practice of consuming brains from deceased family members. Genetic analysis conducted in one of these tribes revealed differences in incubation times between the three genetic subgroups, with the shortest incubation time being discovered in the methionine-homozygotes and the longest in the heterozygotes.[27,28] Research published very recently indicates that heterozygotes can also eventually die from kuru – in some cases after incubation periods spanning several decades.[29]

Genetic modification has been used to produce strains of mice expressing human prion protein.[30] The researchers had access to murine strains for each of the three genotypes (methionine-homozygous, valine-homozygous and heterozygous). Each of these so-called transgenic strains was found to transmit infectious abnormal prion protein. Each strain of sick mice had different pathological characteristics and transmission was most efficient in the mice with the methionine-homozygous prion proteins.[30]

3 Variant CJD and blood banks

This chapter deals with the transmissibility of vCJD via blood transfusion and its consequences. In this report, blood transfusion is understood to mean: the administration of cellular blood products (e.g. red blood cells) to a patient. These cellular blood products must be distinguished from plasma products, medicines made from blood. There is no evidence to date that vCJD is transmissible via plasma products.[8] The same cannot be said of cellular blood products.

3.1 Variant CJD is transmissible via blood transfusion

In 2001 the Health Council came to the conclusion that the transmission of vCJD via blood or blood products cannot be ruled out.[2] The committee that produced the advisory report based this conclusion on the fact that abnormal prion protein had been detected in lymphoid organs and on the results of animal studies available at that time, such as the transmission of BSE via blood transfusion in a sheep.[31] This transmission was subsequently confirmed in several sheep and also observed in a rodent model for vCJD.[32,33]

Transmission of vCJD has meanwhile in all probability also occurred in humans. In 1997 – at which time the transmission of vCJD via blood transfusion was still just a theoretical possibility – a database was established in the UK to record the recipients of cellular blood products derived from people who would later develop vCJD (24 of them were blood donors).[34] Since then, two of those recipients have died from vCJD.[35,36] The possibility that these deaths are unrelated to the blood transfusion received is exceedingly remote.[35] The patients died 6.5 and 8 years, respectively, after having received the blood transfusion. This is relatively soon compared with mortality following dietary exposure.[8] In a third recipient (already mentioned in section 2.3), who died from a different cause, abnormal prion proteins were detected in spleen and lymph nodes.[26]

In a publication about (v)CJD and blood transfusion, staff from the UK National Blood Service and the National CJD Surveillance Unit point out that the current number of infected individuals may be an underestimate.[37] They explain that the number of infected individuals may still rise on account of the long incubation period and also because blood transfusion recipients may have died from other causes before the symptoms of infection manifested themselves.

In order to combat the possible spread of vCJD, donors in the UK (and now also in the Netherlands) who have themselves in the past received a blood transfusion are barred from giving blood.

3.2 Blood tests for abnormal prion proteins are in development

The strong probability that vCJD can be transmitted via blood transfusion has resulted in major efforts to develop a diagnostic test that can be used in blood banks. The aforementioned Western Blot test can only be performed on lymphoid tissues such as the tonsil. This test is not suitable for screening donors as it requires an invasive intervention (tonsillectomy) and the procedure is too time-consuming to be used in a blood transfusion setting. The Health Council therefore advised against the introduction of this tissue test in an earlier advisory report.[2] In actual fact, the committee considering this issue added that testing for an untreatable disease such as vCJD is, in any case, morally problematic.

Worldwide, at least eight university groups and companies are actively developing rapid, non-invasive tests based on the detection of abnormal prion protein in the blood.[38,39] Progress has been so rapid that a test suitable for use at a blood bank is expected to be on the market within a few years.

An alternative approach to the problem of combating transmission of abnormal prion protein via blood transfusion is to remove that protein from blood by means of adsorption. Here too, developments are taking place.[40] At present, however, it seems unlikely that the development of such filter systems will render the discussion over the desirability of a test for abnormal prion protein superfluous.[19]

3.3 Testing for rare diseases is not without pitfalls

Laboratory tests are rarely, if ever, perfect. Virtually every test produces false-positive and false-negative results, and consequently the tested samples are wrongly scored positive or negative. As a rule, tests with better sensitivity (i.e. relatively few false-negative results) will result in lower specificity (a relatively large number of false-positive results). Conversely, tests with better specificity often display lower sensitivity. Since the objective of screening is to ensure the safety of blood and blood products, the prime concern will be to minimise the percentage of false-negative results. However, false-positive results are also undesirable both from the perspective of blood supplies (since more donors are excluded than necessary) and that of the individual blood donor (unnecessary anxiety and unnecessary additional tests). Moreover, when testing for relatively rare diseases in a healthy population – as is hopefully the case when testing blood donors for vCJD – the number of false-positive results is likely to be far greater than the number of true-positive results.[8,13]

This is underlined by the following mathematical model, in which the number of blood donors in the Netherlands has been estimated at 500,000, the prevalence of vCJD has been set at the same level as in the UK (237 carriers of abnormal prion proteins per million inhabitants, see 2.2), sensitivity has been set at 100 per cent and specificity at 99 per cent. If each blood donor is tested once using an assay with these properties, 119 donors will be correctly excluded. At the same time, the test produces 4,999 false-positive results (see table), meaning that there is only a 2.3 per cent chance that a donor with a positive test result actually has abnormal prion proteins in his/her blood (the positive predictive value of the test result).

	Abnormal prion proteins present	Abnormal prion proteins not present	Total
Positive test result (abnormal)	119	4,999	5,118
Negative test result (normal)	0	494,882	494,882
Total	119	499,881	500,000

If a specificity of 99 per cent proves unattainable in practice without sacrificing too much in terms of sensitivity (and this is not unlikely), the number of false-positives will turn out to be higher than these calculations suggest. That means an even more skewed relationship between the donors excluded rightly from making further donations and those excluded wrongly. A lower prevalence – as is probably the case in the Netherlands – has the same effect.

When developing a test, it is customary to assess the likelihood of false-positive and false-negative results by testing large numbers of known positive and known negative samples, derived from patients and controls. This is not feasible in the case of a test for vCJD owing to an acute shortage of available samples from vCJD patients (the 'known positives'). In an effort to overcome this problem, material is used from patients with other prion diseases and from infected animals.

In the case of tests that have been in use for some time, an independent second test is usually employed in order to distinguish between a true-positive and a false-positive result. Although a variety of development programmes are currently under way in several locations, it remains to be seen whether, in addition to an initial screening test, there will soon also be such a 'confirmatory test' and how good this will be. Owing to the long incubation time and fatal outcome of vCJD, plus the fact that a relatively large number of false-positive results can be anticipated, some observers argue that it is not acceptable to start testing for vCJD until an accurate confirmatory test is available.[8,13,41]

3.4 Should such a test also be introduced in the Netherlands?

There will probably be great public pressure to expedite the introduction of a test for abnormal prion proteins in the UK. This is not only because the prevalence is greatest there, but also on account of the problems that have been encountered in the past with regard to screening tests for hepatitis C virus. The introduction of hepatitis C screening began later in the UK than in other countries.[42] This has led to successful damages claims from patients who became infected with the virus as a result of blood transfusions. During a seminar hosted by the UK Health Protection Agency, experts predicted that a test for vCJD would be introduced fairly soon, precisely because of the experiences with hepatitis C virus testing.[19] On the other hand, the Spongiform Encephalopathy Advisory Committee (SEAC), which was set up to advise the UK government about prion diseases, has urged that a test for vCJD must only be introduced once there is sufficient consensus over its reliability.[43] In France and Ireland too, the case for and against testing will probably be debated fairly soon in view of the vCJD cases that have occurred there and the problems encountered in the past during testing in connection with blood transfusions.

Against this background, the Netherlands too will be forced to take a stance on the introduction of the test, partly because its introduction in other European countries may act as a precedent. This effect may be further reinforced if producers of plasma products decide to introduce testing for vCJD for commercial reasons. In the past this phenomenon has influenced the ultimate decision to bar donors in the Netherlands on account of a stay in the United Kingdom.

4 Desirability and acceptability of testing for vCJD

In this chapter we examine the ethical and legal considerations that influence decision-making on the question of whether or not to test donors for vCJD. After outlining the current regulatory framework governing the supply of blood, we discuss the dilemma posed by the possibility of testing.

4.1 Government is responsible and aiming for optimum safety

Blood and blood products are of vital importance to health care. Blood is often, quite literally, life-saving. Owing to their human origin, however, the use of donor blood and products derived from it can also carry certain health risks. These risks apply not only to patients who require a blood transfusion on one occasion in an acute situation, but certainly also to some – especially vulnerable – patient groups who are reliant on blood transfusions (known in the Netherlands as 'polytransfusees') over a period of many years. These include patients with sickle cell disease, thalassaemia and haemolytic anaemia.

Government is responsible for the availability of blood and blood products to those who are dependent upon them and also for their quality and safety. This responsibility arises from government's constitutional duty to take steps to promote public health (Section 22 of the Constitution) and is fleshed out in the Blood Supply Act (Wibv). The task of putting these duties into practice has been entrusted to the Sanquin Blood Supply Foundation (Sanquin).

Government's responsibility has also been established at the international level, initially in a Council of Europe Convention (now nearly 50 years old), and later also in legislation and regulations issued by the European Union. For example, the 2003 Blood Directive sets minimum requirements for quality and safety throughout the blood transfusion chain (collection, storage, processing and distribution).[44] However, Member States retain the scope to operate their own policy in this area.[45]

The basic premise of the Blood Supply Act is that blood supplies in the Netherlands 'must meet high standards of safety and quality'. The Minister of Health, Welfare and Sport has repeatedly emphasised that this does not mean maximum safety, but optimum safety. Clearly, maximum safety would mean that every possible risk must be excluded, regardless of the relationship between the health benefit that stands to be achieved and the costs incurred. Given the limited

financial resources within health care, such an approach cannot be justified.[46,47] In a more general sense, the same message was conveyed in the government's position statement on the RIVM report *Nuchter omgaan met risico's* [Coping rationally with risks].[48,49]

In 2001 the possibility – still just a theoretical risk at that stage – that vCJD might be transmitted via blood transfusion prompted the Health Council to recommend the adoption of general leukodepletion[2], a costly step. This triggered a discussion over the relationship between the notion of 'optimum blood safety' and the precautionary principle, which was also accepted as a protective measure at European level*.[50] This ought not to be regarded as a contradiction, however.[51] Optimum safety does not mean that it is only justifiable to take action once any scientific uncertainty over the precise level of risk has been removed. Conversely, 'precaution' does not oblige government to choose the 'certain' option in preference to the 'uncertain' one whenever it encounters a theoretical risk.

The justification for adopting optimum rather than maximum safety as a policy goal is not based solely on economic considerations. Also important is the fact that the pursuit of the highest possible level of safety can, in itself, jeopardise blood supplies,[2,52] examples being the exclusion of substantial groups of donors and measures that could undermine donor willingness or public confidence in blood supplies.

4.2 Blood donor testing is meant to protect recipients

Testing of donors – and their blood – is performed in order to protect the recipients against blood-borne diseases. It is with this in mind that tests have previously been introduced at the blood banks for hepatitis B and C virus and HIV, alongside a range of other measures designed to ensure the safety and quality of blood and blood products. Because testing of donors serves a third-party interest, this screening does not require donor consent (unlike screening in the context of population screening). That is to say, anyone who does not wish to be tested can, of course, choose not to give blood. However, anyone wishing to give blood must accept that his or her blood will be tested for certain serious, transmissible diseases. The donation itself is voluntary, but it does include testing. An implementation decree to the Blood Supply Act has specified those diseases for which donor blood must, at all events, be tested.

4.3 Testing for vCJD is not in the interests of the donor

The majority of donors do not object to their blood being tested providing the diseases in question are treatable. An unexpected positive (i.e. abnormal) test can even prove beneficial for them if early detection offers opportunities for prevention or treatment. If, however, the diseases are serious and untreatable, a dilemma arises. It then becomes all the more important to protect

* This is usually understood to mean that scientific uncertainty with regard to a serious and irreversible risk cannot justify a decision not to take action. There is still much debate over the question of precisely how the precautionary principle is to be interpreted in several areas. The Health Council will consider this matter in a separate advisory report.

recipients of blood or blood products against the transmission of that disease. The unfortunate corollary is that a positive test result may have extremely far-reaching consequences for the donor.

It is very emotionally distressing to discover being at an increased risk of developing a serious disease which can neither be treated nor prevented. This information may also have negative implications for the person concerned as far as work and insurability are concerned, or lead to exclusion and stigmatisation by other means. This makes screening for vCJD both morally and legally problematic. In other legal contexts, testing for serious untreatable diseases is subject to certain restrictions (Population Screening Act) or even prohibited (Medical Examinations Act) in order to protect people against such results. From this one can infer that great emphasis is placed, from a legal standpoint, on the need to spare people such highly alarming news about their health prospects.*

But what if it should prove necessary to introduce a test for vCJD in order to prevent donor-blood recipients being exposed to a health risk that is probably small but nonetheless extremely serious? Does the fact that there is a major public interest in safe blood supplies mean that one can ask donors to submit to testing for abnormal prion protein, given that the chances of this protein being discovered are probably extremely remote? Or is it simply not justifiable to impose this condition so long as no means of treating or preventing vCJD is available?

4.4 Testing for vCJD can result in donor withdrawal

The argument that it is acceptable to screen donors for serious, untreatable disorders, since the individuals concerned can clearly stop giving blood if they do not wish to undergo such a test, immediately raises a second dimension to the problem. If the introduction of screening were to result in large numbers of donors being deterred from continuing to give blood, this might possibly jeopardise the maintenance of adequate blood supplies.

This too is a moral dilemma. However we are no longer weighing the respective interests of donor and recipient, but the greater safety of donor blood against the importance of having blood supplies at all. If the price to be paid for the greater safety that stands to be gained by screening for vCJD is that insufficient blood becomes available to meet patients' needs then one must ask whether it does, in fact, make sense to introduce such a test. In legal terms, this boils down to the relationship between two constitutional duties of government: not only

* The fact that this principle has a broader application was discussed during the parliamentary drafting of the Population Screening Act (WBO), when the debate centred on whether screening that is performed in pursuance of other legislation would also be subject to the WBO (and, more particularly, its permit requirement). In the Memorandum of Reply, the government stated that this was not the intention: 'It can doubtless be assumed that, when weighing up whether particular medical research ought to be required by law, parliament will also already have weighed up whether that research is desirable in relation to the possibility that the participants may be exposed to undesirable side effects' (Lower House of Parliament 1990-1991, 21 264, no. 5). In actual fact, the exclusion provision that was incorporated in the draft legislation for this very reason (Lower House 1990-1991, 21 264, no. 6) did not find its way into the final wording of the WBO. According to the WBO Committee, however, this has no effect on Parliament's intention on this point.[53]

must it ensure the availability of blood supplies, but it is also answerable for the safety of these supplies (see 4.1).

On a limited scale, research has been conducted in the United Kingdom on donors' attitudes with regard to vCJD testing.[19] It was found that the better informed people were about vCJD, the less certain they were about their willingness to be told of the outcome of any test that might be performed. It is planned to repeat the research as soon as a practical test is available. Needless to say, a further key question to ask is what decision donors will make if a test is actually introduced.

Owing to the awareness that will be generated through the information campaign, one cannot rule out the possibility that the introduction of a test for vCJD might also have implications for the confidence that recipients of blood and blood products have in the safety of these products. The UK HPA emphasises that further research is also needed into this possible effect (fear of infection) and into possible ways of minimising this effect through adequate information.[19]

4.5 Non-disclosure is not a solution

So is it possible to avoid the dilemma outlined above by screening the individuals concerned, but not informing them of the outcome? In this way it should be possible to further reduce the risk of transmission without causing the donor any harm and thereby possibly also undermining his/her willingness to give blood. It is clear, however, that non-disclosure is not a viable option here, not even if one were to have the consent of the individual concerned. After all, a positive result means that the person in question must henceforth be barred from giving blood and it would be difficult to conceal the reason for taking this step.

It is unacceptable, for various reasons, to continue inviting the individual concerned to attend further blood donor sessions and then to discard the blood, even if he/she were to have consented to this in advance. Not only does it expose the donor to the – albeit very small – risk of complications during blood collection without good reason, but it is hazardous for the recipient (since someone might forget to discard the blood), it is a waste of blood, time and resources, and it is contrary to nature and the aim of the blood donation agreement. Moreover, under European regulations prospective donors must be told in advance that they will be contacted if an abnormal test result has health implications for them and also that certain findings lead to exclusion of the donor and destruction of the donation.[54]

Needless to say, the risk of further transmission is another important consideration. Sanquin reports positive tests for notifiable infectious diseases. It is advisable to inform the GP about a positive test result and its significance (with the consent of the individual concerned) and also to make a note to this effect in the medical records.

4.6 Partial introduction does not seem a good idea

Patients who are dependent for their survival on regular blood transfusions are a particularly vulnerable group. Furthermore, the risk of transmission is far greater for them than for patients who occasionally receive a blood transfusion. The question arises as to whether partial introduction might be worth considering (specifically in order to protect this vulnerable group) if it is decided not to test all donors for vCJD for the time being. In practice, this would mean only testing those donors whose blood is used for 'polytransfusees' (see 4.1). That would also mean a corresponding reduction in the loss of donors that might be anticipated in connection with the introduction of a vCJD test. There are, however, considerable drawbacks. Firstly, the proposal is inconsistent with the basic principle that all recipients should be treated equally. After all, every patient faces an equal risk of transmission during each separate transfusion. Moreover, the creation of a two-tier system is a burdensome complication for the blood service. Thus it would appear that partial introduction is not a good idea.

4.7 False-positive results lead to extra anxiety and loss of donors

Since the prevalence of abnormal prion proteins is expected to be low in the Dutch population (or, at any rate, no higher than in the UK), the figures presented in section 3.3 show that there may well be an extremely large number of false-positive results, even if the test is relatively specific (99%).

This problem is further compounded by the possibility that the characteristics of an initial test may be less favourable than has been assumed in that calculation. Consequently, the relationship between false-positive and true-positive results (i.e. the positive predictive value of the test) may in any case initially still turn out to be less favourable. Needless to say, false-negative results may also pose a problem in connection with an inferior test. Consequently, it is not possible to offer recipients an absolute assurance that the blood which they receive will not contain any abnormal prion proteins. Furthermore, some donors will then be wrongly reassured. The biggest problem, however, is the fact that a large number of false-positive results is anticipated. This has far-reaching consequences, especially until such time as a good confirmatory test is available.[55]

First of all, one can envisage consequences for the donors. Even more donors will receive alarming news than would be the case with an optimal test. To this message could be added that this will, in all (or nearly all) cases, be a 'false alarm', but because it is not possible, without confirmatory testing, to say in which cases this will apply, those results may nevertheless give rise to considerable anxiety. For the reasons cited above, it is not possible to avoid informing the person concerned, not even if one were to argue that the result does not have any real bearing on his/her state of health in view of the large number of false-positives. After all, the result will probably lead to the destruction of the donation and the exclusion of the donor, who must therefore be informed. But many recipients will also be caused needless anxiety. Patients may

wonder whether they have received donor blood in the past from a donor who has now tested positive.

Furthermore, account must be taken of the implications with regard to costs and the organisation of care. Precautions that are now already being taken when treating individuals suspected of having vCJD (see 5.4) would need to be extended considerably if a substantial – theoretical – risk group of donors who test positive were to emerge.

Finally, a test with many false-positives inherently poses a problem for the supply of blood, quite apart from the effect on donor willingness, which has already been discussed (see section 4.4). In the latter case, the loss of donors can be regarded as voluntary: donors who drop out because they do not wish to undergo a test for vCJD. The greater the anxiety that a test arouses among the donor population, the more real that risk will be. But because everyone who tests positive must be barred from further donation, a test with many false-positives may also be associated with a considerable involuntary loss of donors. This effect will be further exacerbated by the fact that donors usually give blood several times per year.

4.8 What does 'optimum safety' mean in this context?

The decision-making over the possible introduction of a test for vCJD will inevitably take place under conditions of great scientific uncertainty. It would not necessarily be problematic if it were to be decided that the policy needed to be geared to maximum safety, regardless of costs and other negative effects. However, that position is not easy to justify for the reasons cited above (see 4.1), nor is it the policy of the Dutch government. Furthermore, greater safety is an illusion if the supply of blood is inherently undermined by the introduction of a particular measure.

On the other hand, it is not altogether clear what pointers for decision-making can be drawn from the alternative notions of 'optimum blood safety' and a 'rational safety policy'.[47] Relevant considerations are the cost-effectiveness of testing for vCJD, the question as to whether greater safety for recipients offsets the disadvantages of testing for the donors, and whether the introduction of such a test will significantly undermine donor willingness.

In order to clarify the last point, it is important to survey attitudes among donors (although the question remains as to how people will react if a test is actually introduced). Cost-effectiveness and disadvantages for the donors are considerations that require a clearer understanding of the risk that is to be prevented through the use of a test. Research data are now available in the UK that allow an estimate to be made of the number of people in the population with abnormal prion proteins (see 2.2). No such data are available for the Netherlands. Judging by the number of diagnosed cases of vCJD, prevalence in the Netherlands will probably be lower than in the UK, but we do not know how much lower. Although a better estimate of the risk of abnormal prion-protein transmission in the Netherlands would require further (anonymous) prevalence testing in tonsils and other tissues , that information will not facilitate the decision-making on whether or

not a test should be introduced. After all, the outcome will still be that the risk of transmission is extremely small, but cannot be ruled out.

The seriousness of vCJD is not at issue, nor is there any prospect for the time being of effective methods of treatment or prevention. It is still debatable, however, whether infection with abnormal prion proteins will also always lead to vCJD. We do know that the two patients who developed vCJD following blood transfusions were methionine homozygotes, but it is not known whether all methionine-homozygote recipients will contract vCJD when exposed by this route. Nor do we know how people from the two other genetic subgroups will fare (see 2.3).

A further consideration concerns the incubation period of vCJD that is contracted through blood transfusion. The incubation times in the two cases known to date (see 3.1) were 6.5 and 8 years, respectively. As far as the health benefit to be gained through testing for vCJD is concerned, it is important to establish the relationship between this incubation period and the survival of people who have undergone a blood transfusion.Little research has yet been conducted into this question. The first Dutch data point to a median survival time of 3 to 4 years.[56] Those data are, however, derived from a single university hospital with a specific patient population. Nevertheless, they show that the importance of testing for vCJD varies from one group of recipients to another. Needless to say, this observation does not hold true for individual recipients of blood transfusions, especially not if they belong to specific groups with far longer survival times, such as infants and women during childbirth.

All these subtle distinctions and uncertainties lead back to the fundamental question of what we are to understand in this context by a policy of 'optimum safety'. One can, of course, consider what are regarded as acceptable risks in other policy areas or elsewhere in medicine. At best, however, that may help to put the necessary public debate over what risks are acceptable in connection with blood supplies into a broader perspective.[51] The difficulty here is that a host of affective (and hence less 'rational') factors also have a bearing on the public perception of risk.[57,58] That is certainly the case when considering such a symbolically charged product as blood. Although blood is safer than ever before, the public does not necessarily perceive it to be safe enough.[52]

5 Implications for policymakers and practitioners

This chapter outlines the implications of the availability of a non-invasive test for vCJD developed for use at the blood banks. The introduction of such a test requires support measures, while non-introduction may imply liability. Furthermore, timely consideration is needed with regard to the desirability of testing for vCJD in other areas of healthcare.

5.1 Government and Sanquin have a responsibility of their own

As far as decision-making about whether or not to test for vCJD is concerned, government and the privatised blood supply organisation, Sanquin, each bear a responsibility of their own. Government can decide to include vCJD in the list of disorders for which blood donors must be tested under the Blood Supply Act. In that case, Sanquin would have to introduce the test at the blood banks. The fact that government had not reached this decision, or had decided not to make a test for vCJD mandatory (at least for the time being), would not prevent Sanquin from introducing such a test if it were to deem such a step necessary in order to guarantee the safety of its products. However, it would have to turn to government in order to finance this measure, and to this extent it would therefore probably require consent. Whether government might also be able to prevent Sanquin from testing donor blood for vCJD is a question that requires further investigation.

5.2 Introduction requires a series of support measures

Should a decision also be taken to introduce a donor test for vCJD in the Netherlands, then it will in any event be necessary to take a number of steps to minimise undesirable consequences for donors and others. In this connection, the UK HPA rightly refers to the duty of care that the blood supply organisation has with regard to the donor.[19]

In the first place, there must be a guarantee that the donor will be adequately informed about the test for vCJD and its possible implications. 'Adequately' means that he or she is enabled to make an informed, considered and voluntary decision on whether or not to continue giving blood once donation has become subject to screening for vCJD. The donor must be asked to consent to being informed of the outcome of the test. The fact that this information may lead to donor withdrawal must not be a reason for withholding information. Time and expertise will need to be made available for the provision of this information.

There must also be adequate facilities for expert counselling of donors with a positive test result. Clearly, the quality – or, more accurately, the specificity – of the test, or the lack of a good confirmatory test, has a direct bearing on the necessary scope of this service.

It must be possible to ensure that donors who test positive receive adequate care and are protected against forms of stigmatisation and social exclusion. As far as stigmatisation and exclusion are concerned, one can also envisage possible consequences with regard to work and insurability. It is important that insurers should clarify their policy in this respect. Depending on the actuarial implications of a positive test result, the HPA suggests that it may, at some stage, be necessary to create alternative (non-commercial) forms of insurance, which must prevent people who agree to undergo testing for the benefit of others from experiencing any social problems as a result.[19] In the Netherlands, the Medical Examinations Act (WMK) imposes limits on the rights of employers and insurers to investigate and ask questions. Under this Act, insurers offering life-assurance or disability-insurance policies that fall below the so-called 'question threshold' are prohibited from asking questions about serious, untreatable hereditary disorders and also from enquiring about the outcome of genetic testing. As has been pointed out previously, this provision, which was intended to be a protective measure, may possibly have been too narrowly formulated,[59] since it relates only to genetic disorders. Insurers would therefore be permitted to ask: 'Have you been tested for vCJD and if so, what was the outcome?'. Given the protective purpose of the Act, this would appear to be a significant shortcoming.

The introduction of a test will inevitably lead to a loss of donors. In order to offset the voluntary and involuntary loss of donors, new donors will need to be recruited. During this process, reference can be made to the major importance of having blood supplies based on voluntary donations, but information must also be provided about the possible implications of the test for vCJD that is associated with donation.

If the test is introduced, a certain number of donors (precisely how many will depend on the quality of the test) will be found to test positive, many of whom will already have given blood in the past. It will be necessary to consider whether (and under what circumstances) it is desirable to trace and inform the recipients of these earlier transfusions. This too requires adequate facilities for the information and counselling of the individuals concerned.

In order to protect third parties, it is necessary to introduce measures designed to prevent further transmission of abnormal prion proteins during the medical care of donors who test positive. Depending on the quality of the test, this may mean that the application of the precautionary measures that are already being taken where (v)CJD is either present or suspected[60] will need to be extended considerably.

We must ensure that proper information is available for relatives of donors who have tested positive or others around them. They may be concerned that they have themselves in the past been exposed to the same source of infection. Based on current data, there is no cause for concern

over transmission from mother to child, though it is not possible to provide absolute reassurance.

Finally, the HPA emphasises that the introduction of a test that may at first still be suboptimal carries with it the moral obligation to encourage further research. This should be aimed both at improving the test (so that fewer people suffer harm as a result) and developing alternative methods of preventing the transmission of vCJD in the course of blood transfusions (so that testing would no longer be necessary).

5.3 Non-introduction requires consideration of liability

If the outcome of the decision-making is that a test for vCJD is not introduced in the Netherlands (for the time being, at least) because such a measure would not be consistent with a policy that is geared to optimum safety, or because the negative consequences of its introduction outweigh the positives, the emphasis will shift from the consequences for the donor to the implications for the recipient.

If adverse health effects occur because the donor has not been tested for a particular disorder, then Sanquin – the privatised blood supply organisation – may be held liable. What we are dealing with here is strict liability due to the supply of a defective product (i.e. blood infected with abnormal prion proteins). The two most obvious legal exceptions to this strict liability would appear not to apply. The first exception is that the supply of a defective product was inevitable owing to the need to comply with government regulations. So long as there is no regulation that prohibits Sanquin from using a test for vCJD, this would not appear to be exculpatory. The question of whether government can impose such a prohibition on Sanquin requires further research.

The second exception is that this is a defect that was impossible to identify based on the current level of knowledge. As soon as a practical blood test becomes available, this defence may also cease to apply. Under these circumstances there is thus a real possibility that Sanquin may be liable for any harm that might result from the transmission of vCJD via blood products. Sanquin has taken out insurance to cover the consequences of strict liability (albeit with a large excess in relation to liability for the consequences of vCJD transmission). This insurance may possibly require closer consideration if it is clear that a test for vCJD will not be introduced. This is, indirectly, also a matter for the government to address through its financing of Sanquin.

Whether government can also itself be held liable is less clear. The emphasis would then have to be on liability arising out of tort – and, more particularly, failure to issue regulations which, had they been in place, would have required Sanquin to test blood for vCJD. There is varying case law with regard to government's liability for the failure to issue regulations to prevent adverse health effects (e.g. in connection with the legionnaires' disease in Hoogkarspel). According to this case law, the determining factors include not only awareness of the risk, the extent of this

risk and the seriousness of the possible consequences (and also the possibility of limiting that risk through regulations), but also the drawbacks and (social) costs of risk mitigation measures. Thus there is certain scope for weighing up the advantages and disadvantages of the regulations in question. It is therefore far from certain whether government would be liable for any adverse health effects that might arise from failure to make a test for vCJD compulsory, although this cannot be ruled out. Further reflection is needed with regard to the implications of any liability that might rest with Sanquin and, possibly, the government.51 Consideration will also have to be given to the question of whether, from a moral standpoint, people who contract vCJD as a result of the decision not to test donors for this disease ought not in some way to be compensated.

5.4 Testing for vCJD must also be considered in other areas of medicine

Once a presymptomatic vCJD test developed for the blood banks is in place, it is also possible that a case may be made for the introduction of such a test in other areas of medicine in order to protect patients and care providers against the risk of transmission. Timely consideration of the advantages and disadvantages is needed. This is primarily a matter for the relevant professional groups and patients' organisations to consider. This section briefly identifies the areas concerned and indicates what questions arise.

(Neuro)surgery

There are no documented cases of the classic form of CJD being transmitted via blood transfusion, but this is known in connection with neurosurgical interventions and related therapies.[61] This transmission can occur through infected tissue, but also because it is not possible to clean medical instruments that come into contact with such tissue adequately using the existing decontamination methods.[62] Because some hazardous procedures (e.g. transplantation of dura mater and treatment with growth hormone) are no longer performed (or else they are performed in a different manner), iatrogenic transmission of CJD appears to be on the wane.[6] Owing to the long incubation period, however, some new cases are also still being reported.[6] In the case of variant CJD, however, there is considered to be a greater risk of transmission during surgical interventions owing to the spread of abnormal prion proteins and the involvement of the lymphoreticular system.[63,64]

Various precautionary measures have already been introduced in order to reduce the risk of transmission. When patients known or suspected to have (v)CJD undergo surgery, the Dutch Working Party on Infection Prevention (WIP) recommends that maximum possible use should be made of disposable instruments and materials, and that operating procedures should be adapted.[60] If a good non-invasive test for abnormal prion proteins were to become available, it would be possible to use these costly disposables more selectively and thereby increase the level of protection. Knowledge of the presence of abnormal prion proteins in a patient due to undergo surgery could also improve the level of protection for the surgeon. So far, however,

there are no known cases of surgeons or other care providers being infected as a result of activities considered to pose a high risk of (v)CJD transmission.[19]

Before one can contemplate testing patients, it is necessary to have a test with a high level of reliability. Clearly, it cannot be justifiable to abandon existing precautionary measures until we know precisely what implications a negative test result has for the risk of transmission. Moreover, the fact that a high percentage of false-positive results can still be anticipated does nothing to improve the cost-effectiveness of such measures, let alone the far-reaching implications for patients who receive such a result. As far as reducing the risk of transmission in the surgical context is concerned, it would appear that there is, for the time being, more to be gained from research aimed at improving the methods of disinfecting surgical instruments, which are currently still insufficiently effective.[19]

This does not alter the need for timely consideration of the possible role of a preoperative test for abnormal prion proteins. However, this once again raises awkward moral questions. A key difference between surgery and the blood transfusion context is that anyone who does not wish to be tested will not usually have the option of not undergoing surgery. Whereas blood donors are able to withdraw from the potential risk situation, patients cannot. By making access to a necessary operation contingent upon testing for such an extremely serious, untreatable disease as vCJD, we put the patient in an exceptionally difficult position. If, however, the intervention is only possible under circumstances that pose a risk to others (i.e. future patients or the surgeon), then the patient can be expected to cooperate with measures that reduce this risk to a minimum.

It has been suggested that non-disclosure might offer a solution in this context (as opposed to the situation at the blood banks).[64] It might be possible to reach an agreement with the patient whereby he or she is not informed of the test outcome. Even this would appear to be problematic, however, owing to the risk of further transmission. As in the case of blood transfusions, the possible introduction of a test will, in any event, need to be accompanied by measures designed to provide adequate pre- and post-test information and counselling and also measures designed to protect those patients who have tested positive against stigmatisation and social exclusion.

Transplantation medicine

Besides surgery, transplantation medicine is another area in which debate is needed on the desirability of testing for vCJD. Although there is still no evidence of transmission via tissue or organ transplantation, this possibility clearly needs to be considered. A pilot study has started in the UK with regard to vCJD testing in connection with the use of tissue transplanted from deceased donors.[19] This study involves the use of the aforementioned Western Blot test (in tonsils or brain biopsy; see 2.2), which is now available. Because of the time that it takes to perform this test, however, it is not particularly suitable for testing donors of organs (and certain tissues) which need to be transplanted as quickly as possible. There is, at this point in time,

still no suitable assay for testing living donors of either tissue (bone, skin, stem cells) or organs (kidneys). It might therefore also be possible to use the blood test that is now being developed for blood transfusions in the context of transplantation medicine.

When tissues or organs are donated post mortem, the donor can no longer be harmed by an abnormal test result. In the case of so-called 'living donation', however, a donor test can have the same far-reaching consequences as in blood transfusions. Here one should weigh the presumably small risk of transmission against the benefits of transplantation for the recipient, especially if the tissues and organs to be transplanted are scarce and potentially life-saving.[65] In the case of direct donation (of stem cells or a kidney, for example) involving family members, partners or individuals who are otherwise emotionally attached, it would be possible for the donor and the recipient to discuss whether or not a blood test for abnormal prion proteins is to be performed. This option is not available when tissue donated by living donors for transplantation purposes is distributed through a 'bank'.

When considering the introduction of a blood test for vCJD in living donors, we are confronted with the same dilemma as in the case of blood transfusions. Although the potentially extremely far-reaching implications of a positive result underline the importance of such a test, they may alternatively serve to deter people from making living donations of tissues or organs. Here too the question arises as to how reliable such a test must be before introduction can be considered. If a test were to be introduced then the earlier comments with regard to information, counselling and protection of donors who have tested positive would apply.

5.5 Individual requests for testing require a good test and adequate counselling

It is conceivable that people who have – or believe they have – an increased risk for vCJD may wish to be reassured about the question of whether or not they have been infected. These might be patients who have received blood from a donor who subsequently developed vCJD or tested positive. Or alternatively patients who have undergone treatment using surgical instruments that have previously been used in someone who was later found to be infected or who tested positive.

In a recent article, this situation was compared with that of people with a familial risk of a serious, untreatable, late-onset disorder such as Huntington's disease.[64] Admittedly, there is a significant difference here, in that Huntington's disease is a hereditary disorder, which can therefore be transmitted through reproduction. For people with a familial risk of Huntington's disease the desire to have children is an important reason for undergoing a test.[66] Since there is no evidence for reproductive transmission of vCJD at present, this motive will probably not apply here; or in any event, it is not a good reason for a test. But people may also have other reasons for wishing to shed light on a health threat that is hanging over their heads. Provided careful counselling is available, it is considered acceptable to test people with a familial risk of Huntington's disease.

Essentially, there does not seem to be any good reason why this could not also apply to people with an increased risk for vCJD.

It is probably relevant that a reliable test is available for diagnosing carrier status for Huntington's disease. Moreover, there is no doubt about the significance of a positive test result for the health prospects of the individual concerned. The same cannot, for the time being, be said of vCJD. Until such time as these uncertainties have been resolved, we still have nothing to offer to individuals who wish to be tested.

6 Agenda

Ever since it was discovered that vCJD can be transmitted via blood transfusion, efforts have been under way in various locations with a view to developing a practical test for use in blood banks. It has become clear in this horizon-scanning report that the possible introduction of such a test raises significant moral questions, but also that there is still great uncertainty over many aspects. These include both the extent of the risk that we are seeking to prevent by testing blood donors and the question of how reliable an initial test will be.

It is important that government, together with the blood supply organisation Sanquin, should give careful and timely consideration to the question of whether the introduction of a test for abnormal prion proteins is desirable and if so, what conditions should be imposed (also concerning the minimum quality standard for tests). Besides assessment from a medical and health-economic standpoint, this also requires more detailed ethical and legal analysis. The fact that introduction in other European countries may act as a precedent lends urgency to this assessment.

Under the Blood Supply Act (Wibv), government is empowered to decide that blood donors must be tested for vCJD. However, Sanquin (the privatised blood supply organisation) also bears a responsibility of its own. Clearly, concerted policy development is desirable (also because of such factors as financing and liability).

As far as blood supplies are concerned, the Dutch government aims for optimum, rather than maximum safety. But what precisely is to be understood by this phrase and what bearing does it have on the discussion as to whether or not a test should be introduced for abnormal prion proteins? It is important that the broader public, as well as donors and recipients (patients), should be involved as much as possible in the debate over how safe blood must actually be and how this relates to the perception of acceptable risk in other areas. At the same time, however, we must take care to avoid arousing unnecessary anxiety.

Various bodies in the UK – such as the Spongiform Encephalopathy Advisory Committee and the Health Protection Agency – have examined the desirability of testing for vCJD and also already made their position known on the possible introduction of such tests. It seems appropriate to consider future policy development in the UK when formulating opinions and making decisions in the Netherlands.

As we embark on this decision-making process, there is still great scientific uncertainty over the precise extent of the risk that we are seeking to prevent by introducing a test in the Netherlands. A decision must be taken in the near future on the desirability of conducting further research into particular aspects of the problem. To gain a clearer picture of the prevalence of abnormal prion proteins, one would need to carry out an anonymous survey of tonsils and other tissues, as has already been done in the UK. Furthermore, no research has yet been conducted in the Netherlands into the willingness of donors to undergo a test for vCJD. Such research is necessary in order to assess the loss of donors that can be anticipated if testing were to be introduced.

Decision-making on the introduction of a test for vCJD has a European dimension – not only because introduction elsewhere may act as a precedent but also on account of the desire for exchangeability of blood products. This requires international consultation, which should consider the moral as well as the practical aspects.

The decision to introduce a test for vCJD would require a raft of support measures to protect the donors and other directly affected individuals. This would not only include adequate information and counselling services, but also measures to protect donors who test positive against social exclusion and stigmatisation. We must assess whether and under what circumstances it is desirable to trace and inform the recipients of earlier transfusions with blood from donors who have been found to test positive. For the protection of third parties, steps must be taken to prevent further transmission of abnormal prion proteins to donors who test positive in the course of medical care.

If it is decided not to introduce a test for vCJD (for the time being, at least), it must be accepted that Sanquin (and possibly also the government) may be held liable for any adverse health effects that could have been prevented with a test for vCJD. The precise legal implications in this area require closer consideration. From a moral standpoint, consideration needs to be given to the question of possible compensation for people who contract vCJD as a result of the decision not to test donors.

A test developed for the blood banks may also be useful in preventing transmission of vCJD in other contexts (especially surgery and transplantation medicine). In some cases, this will give rise to similar questions, which likewise require timely consideration.

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Appendix 1

Membership of the Standing Committee on Medical Ethics and Health Law:

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Prof. J.K.M. Gevers, Professor of Health Law; AMC, University of Amsterdam, *Vice-President*
Prof. I.D. de Beaufort, Professor of Medical Ethics; Erasmus Medical Centre, Rotterdam (until 12 October 2006)
Dr. G.C.M.L. Christiaens, gynaecologist; University Medical Centre, Utrecht
Prof. J.C.J. Dute, Professor of Health Law; Erasmus University, Rotterdam
Prof. R.P.T.M. Grol, Professor of Quality Improvement and Control in General Practice; St Radboud University Medical Centre, Nijmegen
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Prof. H. Jochemsen, Professor of Medical Ethics; prof. dr. G.A. Lindeboom Institute (PLI), Ede (from 12 December 2006)
Prof. J.C.J.M. de Haes, Professor of Medical Psychology; AMC, University of Amsterdam
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Prof. G.A. den Hartogh, Professor of Ethics; University of Amsterdam
Prof. A.C. Hendriks, Professor of Health Law; University of Leiden / healthcare lawyer, Equal Opportunities Commission (CGB), Utrecht
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Prof. M.A. Verkerk, Professor of Medical Ethics, University Medical Centre, Groningen
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