National Creutzfeldt-Jakob Disease Surveillance Unit

Please reply to: Western General Hospital, Crewe Road, EDINBURGH EH4 2XU

Clinical Office:
(Department of Clinical Neurosciences)
Tel: 0131 537 2128
Fax: 0131 343 1404

Professor RG Will, Consultant Neurologist (0131 332 GRO-C)
Dr R Knight, Consultant Neurologist (0131 537 GRO-C)
Dr MA Macleod, Research Fellow (0131 537 GRO-C)
Ms. K Estibeiro, Molecular Geneticist (0131 537 GRO-C)
Miss JM Mackenzie, Study Co-ordinator (0131 537 GRO-C)

Neuropathology Laboratory:
(Department of Pathology)
Tel: 0131 537 1980
Fax: 0131 343 1404

Dr JE Bell, Consultant Neuropathologist (0131 537 GRO-C)
Dr JW Ironside, Consultant Neuropathologist (0131 537 GRO-C)
Mrs L McCardle, Chief MLSO (0131 537 GRO-C)

SENT BY FAX AND LETTER

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Dr Patricia E Hewitt
Lead Consultant in Transfusion Microbiology
National Blood Service
North London Centre
Collindale Avenue
LONDON NW9 5BG

Dear Pat

Thank you for sending me a copy of the letter from Professor Doyal.

I think that this is a very important matter and I wish to make one or two responses to his comments and I thought I should, at the same time, set out the arguments which I put forward at our meeting.

In his letter, he says that the original decision as to not informing recipients or donors was based on the premise that this would in no way impinge on their interests, partly because of the uncertainty surrounding the mode of transmission and also because of the lack of a screening or diagnostic test. He goes on to say that the issue of the lack of any effective intervention was also mooted as a justification for non-notification but he discounted this as relevant to any new policy about notification. He goes on in the letter to comment on two particular issues, namely the scientific evidence of transmission by blood and the emergence of a screening or diagnostic test.

THE INTERESTS OF THE INDIVIDUAL

As far as I am concerned, there are four general reasons why an individual might want to know of some risk to their health or the fact that they have contracted some illness. They are as follows:

1. To protect self (for example if one were immunocompromised, one might want to avoid certain infections).
2. To inform and protect others (for example one may wish to inform individuals that they had been exposed to meningitis or HIV and if one were HIV positive one may wish to protect others from infection).
3. Treatment. Clearly, if there were some treatment available which would modify the course of the disease or cure it, then one would wish to take this. (I guess that the whole issue of HIV is rather different now that there are treatments which modify disease process).
4. Prognosis. Even if there were nothing that somebody could do about a particular disease, one might wish to know the diagnosis in order to plan one's life or alter decisions that one is about to make. Even if the prognosis were somewhat uncertain (for example as in multiple sclerosis) there may be a broad range of prognostic information available which allows some decisions to be made.

BACKGROUND ISSUES

I thought I should address the background issues and then afterwards relate them to the above points concerning informing individuals. There seem to be four broad background issues. I list them and discuss them below.

1. <u>The Issue of Infectivity in Blood</u>.

At the moment there is no convincing evidence that there is clinically relevant infectivity in blood in cases of CJD. However, one has to be very cautious in this situation and, in particular, much of the accumulated evidence relates to sporadic CJD or experimental TSE models and, in this particular situation, one is very much concerned about variant CJD which might, of course, behave differently from other forms of prion disease. The TMER Study is obviously part of the very cautious approach that we need to take in relation to prion diseases. While there is no firm current evidence and some doubt as to whether significant blood infectivity is a real issue in clinical practice, it is obviously very important indeed to undertake research to determine whether or not this is true. I accept Professor Doyal's point that if action is taken both in terms of research and also in terms of practice (such as leucodepletion) that this would and should suggest to the public that there is at least some concern over blood infectivity. This does, therefore, pose some problems in suggesting one does not inform people of certain risks because there is "no evidence of infectivity". Having said that, I think that one can distinguish between actions which are taken in general as a precaution and the information that one may wish to give an individual in a certain specific context.

2. <u>Diagnostic or Screening Tests</u>

I think one has to very carefully distinguish between the diagnosis of neurologically symptomatic variant CJD on the one hand and presymptomatic diagnosis of variant CJD on the other. Indeed, such a distinction would apply to other forms of prion disease. If the disease is symptomatic, then diagnosis is a reasonably straightforward clinical matter although, of course, there are specific considerations and unknowns. As far as this study is concerned, the role of diagnostic tests really relates to presymptomatic testing. Two candidate

tests are mentioned in Professor Doyal's letter. The first of these is a blood test and the second is that of tonsil biopsy.

As far as the blood test is concerned, there are possible developments. However, these are still really rather speculative. We have the issue as to whether or not it is possible to develop a reliable blood test and a fair amount of research is still necessary before this can be established. Even when one has a reliable means of detecting cases by a blood test, there are a number of issues which may well take a long time to clarify. For example, it would need a fair amount of work to determine whether or not there could be "false negatives". In addition, if a disease marker can be determined in blood, it is not at all clear at what point in the illness this positivity would appear. I think quite a lot of prospective evaluative work would be required before this issue could be satisfactorily addressed. In other words, even if a blood test were possible to diagnose presymptomatic disease, I suspect that its routine usage is really some way off.

As far as tonsil biopsy is concerned, there are really not a lot of data available for symptomatic variant CJD. However, such data are accumulating and I expect that the role of tonsil biopsy in symptomatic variant CJD will be relatively clear in the relatively near future. However, as far as a presymptomatic test is concerned, there are very great uncertainties - similar to those delineated with respect to blood. Firstly, we have no idea if tonsil positivity arises presymptomatically in all cases of variant CJD. Even if it does, we do not know at what stage of the illness positivity appears. A publication relating to the appendix in one case certainly suggests that positivity may occur in the appendix some months prior to the onset of neurological symptoms, but this is a single case and relates to a relatively short period of time. Although there may be theoretical reasons for supposing that tonsil positivity may occur some considerable time before neurological symptoms develop, we simply do not know this at present. Some may wish to extrapolate from other prion diseases or other species. However, this would be rather unwise as there is a lot of evidence to suggest that disease phenotype may vary from agent to agent and species to species. For example, it is my understanding that in experimental BSE in cattle, infectivity may be found in the terminal ileum (possibly in the Peyer's patches) but that this is seen for a relatively short, transient period. Therefore, even if the tonsil biopsy can be established as a test for symptomatic disease, I think much work is required before it can be properly considered as a presymptomatic diagnostic test.

We also have to be aware that some individuals might develop reticuloendothelial positivity and yet not go on to neurological disease. This could be either because the incubation period between the infection and neurological disease exceeds their life span or else because reticuloendothelial system disease does not always go on to neurological involvement. Again, a lot more research is needed.

I therefore suggest that although there are diagnostic tests in development, the reliable use of these in the presymptomatic setting is really some way off.

3. Treatment

It is certainly the case that no specific treatment is available at present. There are a number of possible treatments in development but whether or not these have any practical application in the near future is rather uncertain.

4. Prognosis

We have a very clear idea as to the prognosis of symptomatic CJD including variant CJD. However, as I have indicated above, we have no idea as to the prognosis of somebody with presymptomatic reticuloendothelial system positivity from BSE infection. It is not, as in the case of MS, a matter of a lot of variable data, but a matter of having very little, if any, data at all.

THE DECISION CONCERNING/INFORMING INDIVIDUALS

1. In terms of protection of the self, it is very difficult to see how informing individuals would actually have any benefit with respect to this.
2. In terms of informing or protecting others, if it were indeed the case that somebody had developing CJD, one would wish to protect others from possible infection. There are concerns about possible infectivity via blood, dental surgery, and general surgery. There are more obvious concerns about neurosurgery and ophthalmic surgery. In relation to the issues being specifically discussed here, the relevant issue is that of an individual's blood not being accepted for donation. This is clearly the most difficult issue in the whole discussion. In some decisions made in this area, some authorities have taken the view that the exposure of the population in the UK to BSE infectivity renders any member of that population as being a potentially unacceptable risk. For example, the sourcing of blood products from outside the UK and the ban on donations from individuals in the USA who have spent a significant time within the United Kingdom. These decisions have been made simply on the basis of the risk of BSE contamination in food rather than that related to blood.
3. Treatment is not really an issue here. Certainly, if there were some effective treatment available then that would change matters. I would agree that the lack of any effective treatment is not, in itself, a major justification for non-notification.
4. In relation to prognosis, the real difficulty is that we have very little if any data at all on prognosis of presymptomatic infection with variant CJD. I fully accept Professor Doyal's point that many terminally ill people need and want information so that they can make decisions about their lives or deaths. The issue of prognosis is clearly very relevant in many medical situations where there is no effective treatment. However, I think it is very difficult to put much weight on this point if there is really no reasonable prognostic information available.

BLOOD VERSUS INFECTED FOOD

As a final point, there are obvious difficulties in making policy decisions (either in relation to practice or research) concerning the theoretical, undemonstrated, risk of infectivity from blood. It is particularly difficult since we do have reasonably good evidence that infectivity has occurred via food and that the population in the United Kingdom may well have undergone a significant exposure to such infection, with actual variant CJD cases resulting. In

other words, decisions about the theoretical risk of blood infectivity must be taken against a background of potentially greater exposure to something with proven infectivity.

As I have mentioned above, some actual decisions have been made on the basis of the exposure of the population to infectivity in food rather than the theoretical risk of infectivity in blood.

This becomes particularly relevant if one really did have a presymptomatic diagnostic test. For example, if it were established that the tonsil biopsy was a good presymptomatic diagnostic test and this were offered to somebody who had received a blood product from somebody who later turned out to have variant CJD, there would be some uncertainty as to the meaning of a positive test. Clearly, it would mean that they had reticuloendothelial system infection. However, it would be an interesting point as to whether this infection had resulted from the blood transfusion or whether it in fact had resulted from earlier exposure to infectivity in food. In other words, a positive test in this context would not necessarily establish that the infection had come through blood. Indeed, on the balance of probability, in certain situations, it might well be viewed that it would have been more likely to have come from infected food.

If one extends this consideration further, one might therefore argue that it would be unreasonable and unfair to offer a presymptomatic diagnostic test to only those who had been exposed to the theoretical risk of a blood product. If such a diagnostic test were available, surely it should be offered on a general basis to the population as a whole. It would seem to me very difficult to restrict the offer of such a test to one group of individuals who had some theoretical and probably low risk of infection and not offer it to a very large number of people who had a probability of being exposed to a known infective risk at some point.

FINAL COMMENT

Professor Doyal states at the end of his letter that all of this needs to be considered against a background of a programme of public education and individual support. I entirely agree with this. However, I think any public education programme with respect to this would have to be very extensive and would cost a great deal of money. While I am not suggesting that it should not be done, it is not a small undertaking. I am not sure how successful public education programmes have been in relation to other matters such as smoking or HIV.

As far as individual support is concerned, if indeed it is the case that individuals are to be informed of the potential risk in the study, then they really do require immediate access to individual support and detailed accurate information. Again, this is something which would need a lot of input and organisation. It is not clear to me who is available to do this at present.

I appreciate that these final comments are practical ones and therefore have no real effect on the principle of this decision. However, I would be concerned that if a decision was made on principle, those who make it are fully aware of the significant practical implications.

I am sorry that this has proved to be a letter of some length. However, I wished to address these points are carefully and clearly as possible.

With best wishes.

Yours sincerely

GRO-C

RICHARD KNIGHT
Consultant Neurologist

cc: Professor R G Will