Interview with Professor Alastair V Campbell on the recent Listener article.

OBR
Readers may have seen the recent article in the Listener which dealt with Professor During's gene therapy research. Please could you outline the events that led to your being approached by the Listener for comment upon this issue.

Professor Alastair Campbell
The article concerned, in part, a recent attempt to carry out gene therapy in New Zealand, which is one that was before a committee called GTAC (Genetic Technology Advisory Committee) of the Health Research Council. I am a member of that committee. Prior to that committee being set up there was a working party on the clinical and research use of human genes which was a working party of the HRC and the Minister for the Environment. So there were guidelines prior to the establishment of GTAC about what would or would not be acceptable in the area of gene therapy.

Soon after the report of the working party was finalised it came to the attention of the HRC that Professor Matt During wanted to put an application to the committee urgently. The reason for this urgency was that the children that he wanted to try a new technique on had a progressive disorder which would only get worse as the months went. GTAC met for the first time early this year and at that meeting had before it an application from Professor During. Professor During is a member of that committee, but of course had to absent himself from the decision making aspect of the committee. He did answer a lot of questions from the committee.

GTAC drew up the report which was sent to the appropriate ethics committee for the area in which Professor During was experimenting (North Health's ethics committee). The ethics committee also heard from Professor During and the parents. One set of parents brought their child into the committee.

The ethics committee decided to ignore GTAC's advice that this research didn't fulfil the relevant criteria and to ask the Health Research Council committee to reconsider the application on the grounds that it could be a safety trial. However the publicity that then came out made very big claims about this sort of therapeutic intervention. Other claims were made about American approvals having been obtained for this study, which in fact had not been obtained, so that whole thing is very controversial. I think the view of the members of GTAC was that their advice had been circumvented and what was in fact happening was an attempt at gene therapy which really was not justified on scientific or ethical grounds.

The proposal now is that in future GTAC would be like the National Advisory Committee of Human Reproduction, in other words it would be a committee that dealt fully with applications rather than being simply an advisory body to ethics committees. Another possibility is that GTAC's approval would be required before an ethics committee can approve such an application, just as SCOTT (Standing Committee on Therapeutic Trials) operates. One of these two possibilities will be probably be followed.

OBR
You mentioned a distinction between therapeutic and safety trials. What does this distinction amount to?

AVC
The idea of a safety trial is that you're not trying to find out whether a substance has in fact any clinical effect, all you are doing is making sure that there are no bad side effects from the administration of the substance, to find out whether the substance is safe. The argument was made that it was too early to trial this as therapy, but it was not too early to check that the substance had no adverse effects. I

think frankly that that was just a device for allowing them to go ahead. I have no doubt that both Professor During and the parents regarded this as a therapeutic attempt and not simply as a safety trial.

OBR

I gather that if a trial is therapeutic then there has to be an acceptable level of benefit over risk. Is this the feature upon which this distinction rests?

AVC

Yes a therapeutic trial has to be beneficial for the participants and a therapeutic trial is not a trial which only benefits some others in the future. A therapeutic trial is one in which there is some chance of benefit to the participants. A lot of people would say that where there is any degree of invasiveness as there was with this procedure that it is not justified to carry out a trial on young children unless you have some indication that it could be of benefit to them. Because these children had been flown from the States, put under general anaesthetic, had holes drilled in their skulls and a substance inserted, this procedure was very definitely intrusive. There was no evidence, scientifically that it would do them any good at all. In fact Professor During's application form made it abundantly plain that any gain was extremely unlikely and that the best that could be expected was a slight slow down in the progression of the disease. You have to ask, even if that were achieved, whether that's benefit, because you're simply postponing an inevitable end.

OBR

One of the things that wasn't quite clear in the Listener article and in other reports about the issue was the degree of impairment which the children were suffering. Is there an issue about the quality of life for these children even if there is some benefit from the procedure?

AVC

Many people have seen at least one of the children on the television. She appeared a bright little child. However both of the children are very severely retarded in their development because of the destructive effect this disease has on the brain. They cannot see properly, they can't sit up, they can't feed themselves, they are behind normal development for a child of that age and all the predictions from the history of the disease are that they can only get rapidly worse until the children get into a spastic state and eventually die. They will not progress as normal children through the next stages of development and there is no scientific justification for thinking that any substance will somehow allow that progression to happen. That was quite clear in Professor's During's own submissions. He didn't make any claims of that kind.

OBR

In the Listener article you said that there was no reasonable expectation of any benefit to the children and it was unacceptable for a research committee to pass this study and would be under any international code of research ethics. One of the things that was interesting in the Listener article was that one of the mothers when talking about the child, said she'd noticed subtle improvements in her child's ability to recognise and interact with her.

AVC

Well, this comes back to the question of science. A proper estimate of whether or not a progression has been made has to have some objective criteria. It is well known that in the assessment of change people who are hoping for the best will perceive things to be better. This is often true in clinical medicine too, where there may be evidence that a person is not able to communicate, but some relatives may hold on for many months to the idea that they are communicating, because they are looking for this. What you need is some sort of scientific endpoint, you need a baseline prior to the intervention and then you need some sort of assessment of whether these children have made any progression beyond the baseline behaviours. Now the parents are saying "we know best, we know our children best" and so on and I'm sure that's how they feel, but I think that its not acceptable for that to be evidence of objectiveness. After all, we are not just talking about these children we are talking about whether it would be justifiable to enrol a whole group of children with this disease in this particular intervention at this stage. The fact that some parents believe there is some improvement constitutes very poor grounds for suggesting that after all this is of therapeutic benefit and actually involving more and more parents in such an endeavour without objective evidence.

> what was in fact happening was an attempt at gene therapy which really was not justified on scientific or ethical grounds.

OBR

The article finished with one of the parents asking who are these clinicians and ethicists to say what we can or can not do with our children and that they were losing sight of the individual's rights.

AVC

The fundamental task of an ethics committee is to take an objective look at the risks and benefits of any particular intervention. It is very clear in the New Zealand guidelines for ethics committees that the first responsibility of an ethics committees is the protection of the participants in research. These children are unable to volunteer themselves for this highly speculative sort of experimentation. Therefore, the people who have to decide whether its right to involve them in this sort of intervention have to be people who can take an objective look at the risks and benefits involved. It was a unanimous view of GTAC that the balance of risks and benefits was unfavourable. You can say that this is scientists and ethicists speculating in a room if you like, but I think that eventually it's the protection of children that matters. This can only be done by people who are able to stand back a little from the situation and look at the objective evidence.

It seems to me that eventually it is the responsibility of the researcher to say to people who are pressing for something that "this is too soon , I haven't got yet the scientific evidence that would enable me to show that this would be able to be any good for your children and till I do, its not responsible for me to pursue this". I believe that a researcher should do this and it shouldn't be a committee that's blamed for being bureaucratic. Eventually it comes down to the ethics of the individual researcher. But it seems that committees at times do have to be strong, and stop the researchers from rushing in to things.