EXHIBIT 15

PART 1 OF 2

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TRANSCRIPT
OF PROCEEDINGS

FEDERAL COURT OF AUSTRALIA

VICTORIA DISTRICT REGISTRY

HEEREY J

HEARING

No VG 868 of 1995

GENETICS INSTITUTE INC

and

KIRIN-AMGEN INC

MELBOURNE

10.15 AM, MONDAY, 11 MAY 1998

DAY SIX

Continued from 8/5/98

MR B.N. CAINE appeared on behalf of the applicant

DR A.C. BENNETT SC, with MS K.J. HOWARD, appeared on behalf of the respondent

HIS HONOUR: Yes, Mr Caine.

MR CAINE: Your Honour, the position is now that I seek to call Dr Haselbeck as our next witness.

<ANTON GABRIEL HASELBECK, affirmed [10.20 am]

<EXAMINATION BY MR CAINE

Before I introduce Dr Haselbeck's affidavits into evidence in the normal way, my learned friend has a formal objection she wishes to put. It might be appropriate she raise that at this juncture.

HIS HONOUR: Yes.

DR BENNETT: There are two bases for the objections to Dr Haselbeck's affidavit. The first is that we say he wasn't the skilled worker in the relevant art at the relevant time, and the second is that he annexes a number of publications, all of which post-date even 1985, so we object to the relevance both of his evidence and of the publications that he puts in.

The course my friend and I are adopting with objections as to relevance, is, generally speaking, that the objections are made - your Honour probably couldn't rule upon those at this stage - but if those objections could be noted and presumably what your Honour will do is admit the evidence subject to relevance and that can be dealt with in submissions.

HIS HONOUR: Thank you. The objection will be noted.

MR CAINE: Dr Haselbeck, do you have a copy of court book volume 4 with you in the witness box?---Yes, I do have.

Could I take you to page 612 of the court book and could I ask you to indicate for His Honour your full name and address?---My name is Anton Gabriel Haselbeck and I am German citizen and I reside on Baerenmuehlweg 50 in Weilheim, Germany.

Could I ask you to spell for the benefit of the transcript writers your middle name?---Gabriel, G-a-b-r-i-e-l.

Is the address that you have referred to the one that is set out on the first page of your first affidavit at court book page 612?---That's correct.

Whilst you are on page 612, could I ask you, is that an affidavit that you have sworn in these proceedings?---Yes.

Can I take you now to court book page 625. You see there an affidavit sworn 3 July 1997?---Yes.

Is that the second affidavit which you have sworn in these proceedings?---It is.

EXHIBIT #E - AFFIDAVIT AFFIRMED BY ANTON HASELBECK 7/8/1996

EXHIBIT #F - AFFIDAVIT AFFIRMED BY ANTON HASELBECK 3/7/1997

<CROSS-EXAMINATION BY DR BENNETT

Between August of 1983 and July of 1985, you were carrying out post-doctoral work at the University of California at Berkeley, weren't you?---Yes.

That was the department of biochemistry?---Yes.

After that, did you go back to be an academic lecturer at the University of Regensburg?---Correct.

The curriculum vitae that you have annexed to your affidavit doesn't actually, with respect, give very much information. What was the topic of your PhD thesis?---Topic of my PhD thesis was characterising a special reaction connected to the biosynthesis of glycoproteins within the cell.

What cell?---I did my work with yeast cells, but this is a reaction which takes place in all eucaryotic cells - - -

HIS HONOUR: Dr Haselbeck, if you would try to be as slow and clear as you can with technical terms for the purposes of the transcript?---Yes.

DR BENNETT: Did you continue your work on yeast cells in your post-doctoral work?---I did.

You are working for Boehringer Mannheim?---I am.

Are you the head of the department that is concerned with the characterisation of therapeutic human proteins for Boehringer Mannheim?---I am.

Boehringer is a licensee of Genetics Institute?---Yes.

Boehringer has applied for approval in Australia for the marketing of the commercial product that Dr Fritsch described in his evidence, or GI's - - -?---Boehringer has applied for approval of the product which is produced in Germany by Boehringer Mannheim under a licence from GI.

Boehringer wishes to market this product in Australia?---I think so.

It has applied for marketing approval, has it not?---To my knowledge, yes.

The work that you do is really dealing with proteins after they have been isolated; is that correct?---This is correct.

Are you yourself a molecular biologist?---Yes.

Were you a molecular biologist prior to July 1985?---Yes.

Have you yourself ever carried out expression of glycoproteins in mammalian cells?---I never did.

Have you yourself ever tried to clone a gene and express a product from that gene using mammalian cells?---No.

Before 1985, had you yourself ever made or used an expression vector?---Yes.

Prior to July 1985, had you ever made or used an expression vector for the purpose of cloning in mammalian cells?---No.

Have you yourself ever amplified the expression of a gene in CHO cells using the DHFR minus gene and methotrexate?---Not myself.

Have you ever purified a recombinant protein that has been expressed in mammalian cells?---I was involved in the purification. I did it not myself, but people in my department.

Was that work done prior to 1986?---No.

Is it fair to say - and I am quoting the words from paragraph 1.2 of your first affidavit - that the diverse aspects of glycoproteins that you were concerned with up to February 1988 did not include the expression of mammalian glycoproteins in mammalian cells?---Are you referring to my own work?

Your own work?---I did not understand your question.

Is it fair to say that the diverse aspects of glycoproteins that you were personally concerned with up to February 1988 did not include the expression of mammalian glycoproteins in mammalian cells?---Yes.

You yourself did no work on erythropoietin before 1988?---That's correct.

Now, your CV doesn't mention any publications. We have ascertained about a dozen publications that have your name on them as an author; would that be correct?---Probably some more.

Is it fair to say that your publications from 1980 to 1989 were on - I am going to give you three main topics: the glycosylation of proteins in yeasts; on enzymes involved in glycosylation pathways in yeast; and on the location of these enzymes in yeast?---That's correct.

Then is it also fair to say that up to 1990, your own publications were not on the culture of mammalian cells?---That's correct.

They were not on the purification of mammalian proteins?---Correct.

They were not on the analysis of carbohydrates of mammalian proteins?---That is not correct.

Up to 1990, do you say that - - -?---Could you be more precise which publication you're referring to?

I am just asking you whether you had any publication up to 1990 on the analysis of carbohydrates of mammalian proteins?---I think I had a publication, maybe it was 1990 or 1989, where we mention the use of new methods for analysing glycoproteins and this work included also mammalian glycoproteins.

Prior to 1990, were you yourself the author of any publications on recombinant DNA technology in yeast or mammalian cells?---Yes.

Prior to 1990, were you yourself an author on any publication on the expression of recombinant proteins in mammalian cells?---No.

What I am going to show you, Dr Haselbeck, is a bundle of publications of which you are the author or named as an author. Could you please point within those publications to any - that is prior to 1990 - that is on the analysis of carbohydrates of mammalian proteins?---Including 1990 - I was referring to this publication in 1990, "Structural Characterization of Glycoprotein Carbohydrate Chains", that's the one I was referring to in your earlier question.

That's the one you were referring to?---Yes.

Perhaps I can read it on to the record. It is published in Analytical Biochemistry 191, 25-30 (1990) headed "Structural Characterization of Glycoprotein Carbohydrate Chains by Using Digoxigenin-Labeled Lectins on Blots". You said that prior to 1990 there was a publication on the expression of recombinant proteins in mammalian cells. Would you care to identify that one?---Which one are you referring to?

You said that prior to 1990, you did have a publication where the subject matter was the expression of recombinant proteins in mammalian cells?---I said no, I did not - - -

Sorry, my mistake, Dr Haselbeck. Prior to 1990, I think you said there was a paper on the recombinant DNA technology in yeast or mammalian cells. Can you identify that paper?---Yes, that's the 1989 paper, "Purification of GDP massose:dolichyl-phosphate mannosyltransferase".

Perhaps I can read that on to the transcript?---And there is a following - - -

HIS HONOUR: Just a moment. I think Dr Bennett wanted to read that title.

DR BENNETT: This is a 1989 paper published in the European Journal of Biochemistry, and it has underneath that, FEBS 1989, entitled, "Purification of GDP mannose:dolichyl-phosphate O-B-D-mannosyltransferase from saccharomyces cerevisiae". Did you wish to refer to another paper?---No, I was originally thinking of another publication, but that probably was '91.

DR BENNETT: I tender that bundle of Dr Haselbeck's publications.

EXHIBIT #3 - BUNDLE OF PUBLICATIONS BY DR HASELBECK

DR BENNETT: Going for a moment, Dr Haselbeck, to the paper in Analytical Biochemistry, that was not a paper that itself concerned animal cell culture?---That's correct.

Or expression?---That's correct.

Or recombinant DNA?---That's correct.

In that paper, you didn't purify the protein yourself, did you, you received it from another source?---I received it from another source, that's correct.

Just looking at the other paper, the paper from European Journal of Biochemistry 181, that paper concerned the purification of native enzymes from yeast, didn't it?---Right.

It was not a paper concerned with animal cell culture?---No.

Or expression?---No.

Or recombinant DNA?---No.

Is it fair to say that in each of these papers, you gave information that you believed was sufficient for defining and explaining to your readers the procedures used?---I did.

And you also gave information that you believed was sufficient for the identification of the relevant proteins during purification?---As far as this publication was concerned with.

In the paper, the 1997 paper, in the Journal of Mass Spectrometry, I think it is noted on the front of that paper that it was received on 1 April 1997. Would that be right, down the bottom of the right-hand corner?---Yes.

You cite the fact in that paper that recombinant erythropoietin had been made

available as a recombinant protein, if you look at the second paragraph of the introduction?---Yes.

And you cite two references for that?

HIS HONOUR: Whereabouts in the first column?

DR BENNETT: First column, "Human EPO is a protein of 165 amino acid residues. It was first purified from the urine of aplastic anaemia patients and has been made available as a recombinant protein 2 and 3". Do you see that?---Yes.

The references 2 and 3, if you go to the last page, 2 is the Jacobs paper?---Yes.

And 3 is the Lin publication in PNAS?---Yes.

You don't say there, do you, that there was any difference between the two available glycoproteins?---I don't say this.

And you don't warn the reader of your paper that you have a conclusion that the Lin paper reported a protein that was unusual in any way?---The Lin paper, to my knowledge, does not report a protein which is unusual.

And this paper was submitted by you after the date of the swearing of your first affidavit in these proceedings?---Yes. Let me see. No, it was before. This was before. It was submitted in April - okay, you're right.

The first affidavit was sworn in 1986?---Yes.

HIS HONOUR: 1996?---1996.

DR BENNETT: I can't even say I read that wrongly - 1996.

Dr Haselbeck, yeast is a eucaryotic cell, isn't it?---Yes.

But it is not a mammalian cell?---It is not a mammalian cell, correct.

Unlike procaryotic cells, bacteria, all eucaryotic cells glycoslate proteins?---All do.

But you would agree that it is important to recognise that yeast glycosylate differently to mammalian cells such as CHO cells?---That's correct.

In that regard, it is fair to say, isn't it, that you can't extrapolate from yeast to mammalian cells in terms of glycosylation patterns?---Not necessarily.

It was well known as at 1985, was it not, that yeast produced glycosylated proteins that were unlike mammalian proteins?---This was well known.

And it was well known that yeast glycosylated proteins frequently had high levels of mannose?---That was well known.

You knew that yeast glycosylated differently to mammalian cells in 1985?---Yes.

And you know it today?---Yes.

Is it fair to say that the first publication on which you are named as an author, that dealt with erythropoietin, was in 1990?---I think so, yes.

That is one of the papers in this bundle?---Yes. There could have been - I think there was one earlier in '89, which is not included here. You missed it.

Sorry. We did our best. Dr Haselbeck, are you telling this court that as at the date of swearing your affidavits in August 1996 and in 1997 and today, that you are maintaining the position that the carbohydrate data on page 65 of the Kirin-Amgen application are correct?---There is nothing in this specification, this application, which would tell me the opposite.

I am not asking you that question. Are you maintaining the position in each of your affidavits and today that those data are correct?---As it concerns the product as described in example 10, yes.

You are maintaining that those data are correct?

MR CAINE: Before we go any further, I think we have had this debate before, but there is an important distinction between whether or not the witness is being asked whether the data is correct now or at some earlier date. My friend lumped all three together. She may get a negative answer to one and a positive to another. It should be made clear.

DR BENNETT: Are you maintaining here in this court today, Dr Haselbeck, that the carbohydrate composition data on page 65 are correct?---The carbohydrate composition data in example 10, the ones you are referring to?

Yes?---Are correct in a way. I am not really saying that that the absolute numbers are correct, but this difference being established with this numbers are still correct to me with all what I have seen so far. I have not seen anything else which would tell me that they are not correct.

Dr Haselbeck, you were present in court, were you not, during the cross-examination of Dr Fritsch?---I was.

Might Dr Haselbeck please be shown exhibit EFF 23. You were present in court, Dr Haselbeck, when Dr Fritsch was cross-examined about this document?---I was.

And you heard me ask him questions about what was contained in this document?---Yes.

And you heard his answers?---Yes, I did.

Have you read this document before; before right now?---I have not read it before.

Please read it to yourself?---Yes.

HIS HONOUR: That is page 43?

DR BENNETT: Page 42 and page 43. The earlier pages are just introduction.

Have you read that?---Yes.

You heard me ask Dr Fritsch questions about those statements?---I did.

And you also read the affidavits of Doctors Gleeson and Redmond, who were expert witnesses, who have sworn affidavits in these proceedings?---I did.

Having heard the evidence of Dr Fritsch and having read those affidavits, do you still maintain that, in your opinion, the carbohydrate composition data on page 65, referring to example 10, are correct?---Yes.

Could you please name me one example of a mammalian protein expressed in a mammalian cell that has a hexose ratio of the order of 15.09?---I cannot precisely mention one example.

Can you name any report of any mammalian protein expressed in a mammalian cell that has a hexose ratio of over 5?---I don't recall, but I think it's possible to get a hexose GlcNAc ratio of over 5.

HIS HONOUR: A hexose what ratio?

DR BENNETT: A hexose ratio.

HIS HONOUR: I thought there was some added word?---Hexose GlcNAc, that's the other sugar that hexose is related to, N-acetylglucosamine.

DR BENNETT: That is commonly called GalNAc, isn't it?---GlcNAc.

Can you name any publication in which a mammalian protein has been reported expressed in a mammalian cell that has a hexose ratio of over 5?---I cannot.

You are aware now that data have established that if the data on page 65 of the application were correct, that would mean that the hexose value exceeds the value reported in the scientific literature for recombinant EPO by a factor of

nearly 10?---I am aware that data have been established with erythropoietin from CHO cells later on, later than the end of 1984, from 1985 on, which are different from this number, I am aware of this, and they are different by a factor of 10, that's correct.

Are you aware that the total carbohydrate content reported exceeds the weight of the sample itself?---This is not contained in the specification.

I have asked you, sitting here today, Dr Haselbeck, what your opinion is. Are you aware, sitting here today, that the total carbohydrate content reported exceeds the weight of the sample itself?---I am aware of data from laboratory notebooks which indicates that the carbohydrate content is higher than the total amount of protein, yes.

And that would be impossible, wouldn't it?---That is not impossible.

You say the matter could have been manufactured during the course of the experiment?---Not manufactured. Should I explain this?

Do you say it could be a contaminant?---It could be a contaminant, that's true. It's a possibility which always has to be excluded when you analyse a protein or any sample. But there are other explanations. I am happy to give you some explanations, if you wish.

All right. How do you say that the total carbohydrate content reported can exceed the weight of the sample you put in?---Yes. The way this was done, and I am referring to what I was reading in the laboratory notebooks of Dr Lin and Dr Yu, these are the two persons who were involved in the carbohydrate analysis. The protein sample has been purified by Dr Lin at Amgin and sent to Dr Yu for performing the carbohydrate analysis. Dr Lin obviously calculated the protein content by determination, the absorbance at 280, that's a way to determine the protein. You are not measuring the carbohydrate content, just the protein part, and those things in those days were not done very precisely. So it could be that this determination was way off the true carbohydrate or glycoprotein content, and the glycoprotein consists of protein and carbohydrate. By this method, you measure only the protein and even this could be way off the true value. Dr Lin has sent his sample to Dr Yu for performing the carbohydrate analysis. I have not seen any indication in the laboratory notebooks of Dr Yu that he reanalysed the protein content of the sample. He did what probably most people did and still do when they receive the sample, he just hydrolysed the total glycoprotein, that means he cleaved the total glycoprotein into individual parts where it is made off to get the individual sugars and analysed the sugars. Then he added up what he had found as a total amount of sugars, and by doing this he came up with this high number, which is higher as what was originally calculated based on the 280 absorption by Dr Lin. So for me, it is not an impossible thing to have a higher number on one side compared to the lower number on the other side. I think this two analyses didn't fit together because they were not done by the same person.

But you would agree, would you not, Dr Haselbeck, that if you add together the fact that the figure reported for the hexose ratio is unknown and would have been unknown as at 1985 for any mammalian protein expressed in a mammalian cell, plus the fact that there was this discrepancy in the weight of the sample that we have already talked about, plus the fact that the data, if correct, would mean that the hexose value exceeds the value reported for any recombinant EPO by a factor of nearly 10 - that the most likely conclusion is that the carbohydrate composition data on page 65 is incorrect?

MR CAINE: Your Honour, this must be as at today.

DR BENNETT: Yes, as at today.

WITNESS: You said 1985.

DR BENNETT: I think I said what was known at 1985. All right. As at today?---That's a big difference when you're talking about what we know now because you said - - -

Take the question as at today?---Okay. By knowing all carbohydrate data and carbohydrate structure data of the recombinant erythropoietin of today, and I clearly can say this is a very unusual structure which cannot be made, but this is by knowing the carbohydrate structure of recombinant proteins produced after '85. At the priority date, nothing was known about the carbohydrate structure of erythropoietin, nothing.

Let's take that in two steps, before I go on. In giving the explanation that you gave earlier as to how you could get more out than you had put in, you assumed that Dr Lin's calculations were wrong?---I assumed either his calculation or the calculation by Dr Yu could be in quantitative manner, a little bit too high, both could add up and then you get this high value.

That is speculation on your part?---This is not only speculation. As Dr Yu's determination is concerned, he indicated on one of his lab notebook pages, the ones I have seen, something like estimate protein content as estimated by 280, something like this. I don't know exactly the words.

Can you point to any evidence that Dr Lin's calculations were wrong?---That's what I am just mentioning.

Dr Lin's - - -?---I am talking about Dr Lin. I was talking about Dr Lin.

You say that there is evidence in Dr Lin's notebooks that his calculations were incorrect?—There is not evidence that they are incorrect, there is indication that he made just a rough calculation and not a precise protein determination which is not done by 280 measurements, but done by other means, like an amino acid analysis or whatever, to give you a precise number. When we are talking about

comparing the carbohydrate numbers to the protein numbers, you need to have exact numbers for the protein part, otherwise this would not make any sense.

Do you say that the conclusion that you are drawing, and finding reasons for possible explanations, is more likely than the conclusion that the data was simply incorrect?---I didn't understand your question. Could you repeat it, please.

You have given a possible explanation which relies upon a number of errors that would have had to have been made by Dr Lin and/or Dr Yu. Are you saying that that explanation is more likely than, for example, there was simply a contaminant present?---I am not saying this.

In talking about the differences between now and 1985, you commented on that. Prior to 1985, had there ever been a report in the scientific literature of a mammalian protein expressed in mammalian cells that had a hexose ratio of more than 5?---I am not aware of it, no.

As at 1985, you would agree with me, would you not, Dr Haselbeck, that the first thing that would have hit you, if you had seen a hexose ratio of the order of 15.09 for a mammalian protein expressed in a mammalian cell, is that the most likely explanation is that that was wrong?---No, not necessarily. It depends on which context you see these numbers. If you see this numbers in the context of a patent specification and especially in the case where a claim, a precise claim, is based on this numbers, I would not clearly say this is wrong. I would clearly say or think to myself there must be some basis for this numbers, especially the difference between recombinant and urinary EPO, which has been established by using this numbers and also the SDS page and deglycosylation assays. That is what I would have thought.

So are you saying that your immediate conclusion, that if you saw on page 65 a description of a hexose ratio of 15.09 for a mammalian protein expressed in a mammalian cell, that you would have made the immediate assumption that that must be correct; are you saying that?---I am not saying this. I am saying that this is a strange and unusual number, but at this time nothing was known about the expression of a highly glycosylated protein even in a mammalian cell, and I would have had my doubts about this numbers, but together with a lot of other information which is contained in the specification, and because a claim is based on it, a claim which says, having a different carbohydrate composition, I would have thought there must be some basis to this and the analysis must have shown the correct values; more or less correct values.

Dr Haselbeck, you would have assumed, would you not, that different carbohydrate composition simply referred to the fact, as between a mammalian glycoprotein expressed in a mammalian cell other than human, and a human glycoprotein, that the difference would clearly relate to the fact that it was known and expected that glycosylation would be different in CHO cells than it would be in a human cell?---It was not necessarily expected that it would be.

You said "expected"?---I did. I say no, it was not expected that it must necessarily be different.

Are you saying that you would expect the glycosylation pattern from a CHO cell to be identical to the glycosylation pattern of a protein in a human?---I would have not had any expectation at this time concerning erythropoietin.

That is because you had no experience at that time in any mammalian cell expression of mammalian proteins; is that correct?---This is not correct. I didn't have personal experience, but I followed the literature, I knew what was known about glycosylation in mammalian cells.

Then you knew, did you not, that the reported glycosylation in mammalian cells all went to the fact that the glycosylation patterns in CHO cells was different from the glycosylation pattern in human?---I - - -

If you kept track of the literature, Dr Haselbeck, you would have been aware that the reports of glycoproteins was that the glycosylation pattern in CHO cells was different when proteins were expressed in CHO cells compared to when they were expressed in human cells?---There were no reports on erythropoietin.

No, glycoproteins generally?---And there were only a few reports up to '83. There were not many reports about glycoproteins being expressed in mammalian cells, and at this time, certainly not everything was established as it is today. The glycosylation machinery in CHO has been elucidated in the end of the '70s, that's correct, but that does not exclude that this could not make other carbohydrate structures.

But your conclusions would have been based upon the available information, would they not?---Yes.

Can you name me one report prior to 1983 of the glycosylation pattern of a protein that was the same in human and in CHO cells?---I am not aware if there was any report where there has been a direct comparison between the human and CHO expressed protein up to 1983. At least I am not aware of it.

Of course not. You still say today, do you, sitting here in this witness box, or sitting at that bench that you are sitting at there, that even after hearing Dr Fritsch, after reading the information set out in the brief that was submitted by Genetics Institute to the US Patents and Trademarks Office, having read the affidavits of Doctors Redmond and Gleeson, who are experienced in the expression of mammalian glycoproteins in mammalian cells, you still sit here today and say that as at today, you maintain that those carbohydrate composition data are correct?---Yes. As they are presented here in the specification, and I have not seen anything to the contrary concerning this product described in example 10. This is all what I am talking about.

You include in that the very material that was relied upon by Genetics Institute to come to the conclusion that the hexose value reported in the patent is totally invalid?---I do not include this, because GI included in this evidence data obtained from samples which have been used for the PLA.

Dr Haselbeck, you're sitting here today - I am not asking you what your opinion was before - with all of the information that you now have, including everything set out in EFF 23, which includes the conclusion by GI that the evidence is overwhelming that it is invalid, you still say, sitting here today, with all of that information, that it is your opinion that it is valid?---My opinion is the following: when all this evidence is based on what has been determined later on of EPO products used then for the commercial purpose. All what I am saying is the erythropoietin product as characterised in example 10 has these numbers as they are presented here, and I cannot see anything to the contrary, that's all what I can say here. I can say the product which has been developed later on by Amgen does not fit to these numbers, that's correct.

So you do not agree with the formal submission relied upon by Genetics Institute that the evidence is overwhelming that the hexose value reported in the patent is totally invalid?

MR CAINE: Your Honour, I think they are at cross-purposes here and my friend needs to make this clear. There is evidence being given by the witness that the product that Amgen now produces does not fit with the numbers reported. That doesn't deal with the question of the recombinant product, which is referred to in the specification. It is not going to establish they're to be equated, your Honour.

DR BENNETT: I appreciate my friend is trying to put his own position forward, but I am referring now, in EFF 23, to the assertion that the evidence is overwhelming that the hexose value reported in the patent is totally invalid; do you agree or disagree with that?---I disagree with that.

Do you agree or disagree that the analysis performed at Dr Lin's request by Dr Yu of Yale University and the Yu analysis is, on its face, invalid; do you agree or disagree?---I disagree.

Do you agree or disagree that the Lin carbohydrate composition disclosure is plainly incorrect?---I disagree.

You would agree with me, would you not, that Dr Fritsch had more experience than you did on the expression of mammalian proteins in mammalian cells?---I agree, yes. But that does not mean he had more experience in the carbohydrate area.

You heard Dr Fritsch say that before this submission was put into the US Patent Office, that he consulted with other scientists at GI?---Yes, I heard this.

On the question of carbohydrate composition data?---I believe so.

And that the conclusion that was put in this document to the Patent Office, you would accept it would have been a considered submission by Genetics Institute to the US Patent Office?---I think so.

Did you yourself read Dr Yu's deposition?---No, I have not.

You have never read it?---Maybe partly. I certainly have not read the whole deposition.

Were you aware that Dr Yu has admitted that his laboratory's data were wrong?---I am not aware of this.

You never bothered to find that out?---I did not have all this information.

Are you aware that Dr Yu filed a declaration in the United States interference that said that his laboratory's data were incorrect?---I am not aware of this.

I withdraw that. Are you aware that Dr Yu, in sworn evidence, said in the United States proceedings that his laboratory's data were wrong?---I am not aware of this.

Would that make a difference to your conclusion, as at today?---That could make a difference, certainly. Excuse me - - -

Is it fair to say that what you are seeking to do in your affidavits is to assume that the carbohydrate composition data are correct and then to find possible theoretical reasons for how such a result might have happened?---Yes.

Is it also fair to say that all the papers that you rely upon to establish that proposition, save for two that I will come to that relate to in vivo effects of the removal of sialic acids, are well after 1985?---That's correct.

And therefore that information would not have been available to a person as at 1985?---No, I used this information as of '96 to explain why you could come up with a strange carbohydrate composition number.

You have annexed a number of papers in an attempt to show that the glycosylation pattern of a particular protein can be influenced by a number of factors, including ammonium ion concentration or the addition of particular hormones?---Yes.

None of those papers - and I am talking specifically about AGH 3 and 4 - were published prior to 1990, were they?---I don't think so. I don't recall the exact publication.

Please feel free to check. Do you have your affidavit there, the dates of

publication of any of the papers that I am going to refer you to. If you go to AGH 3, it is a review published in May 1990?---That's correct.

AGH 4 is another review - I think you refer to it in the body of your affidavit?---It is 1991.

You would agree with me, would you not, that in each of those papers, it is clear that the purpose of the studies was to show these effects?---The purpose of this two reviews is to put all the information together which was available up to 1990 in respect of 1991 to explain differences in carbohydrate structure, glycosylation in general, connected to different variables.

Yes. And the variables were those that were deliberately altered in the culture conditions in order to induce the effects reported?---Yes. But if you don't do this deliberately, you will never find out. That's the normal research, how these things are being established.

But in each of these reports, there was a deliberate step taken to study such things as unusual ammonium ion concentrations?---I don't think that was unusual. I think they studied normal - they used normal additions or they left out different things. It was not unusual, complete unusual situation, which has been duplicated here as you're referring to.

They deliberately added excess ammonium ion concentration, for example, in order to see the effect?---They could have added excess or just the normal amount of ammonium ion. I don't know.

When they looked at the effect of particular hormones, they specifically added the particular hormone to the culture conditions?---I think so.

You would agree with me that the reports referred to in the review, in which these studies were done, were all post-1985?---I am not aware of all the literature - they are referring in the review, that would take a long time.

Check?---Do you want me to check all the references?

If you wish to? What I am putting to you is the proposition that the review cites references as to these effects that post-date 1985?---If I am just going through the references, I mean the first one is - - -

No, you would have to link back the particular citation as to a conclusion?---What do you mean?

DR BENNETT: That perhaps can be done later, your Honour. It will take too long.

MR CAINE: It is oppressive in these circumstances to ask the witness to go through several pages of references and tie any reference back. He simply can't

do it in the witness box, your Honour.

HIS HONOUR: It is apparent on the face of the paper, isn't it?

DR BENNETT: Very well, your Honour.

You would agree with me that while something like ammonium could be a usual ingredient, that what was done in this work was to put it in in unusual concentrations to see the effect of it; the effect attributable to it?---I don't recall if the concentrations were unusual.

You would agree, by the way, wouldn't you, Dr Haselbeck, that it is clear from the reviews that the differences in carbohydrate structure affect the clearance rate of the protein in the circulation?---It can affect.

And that the major effect of the carbohydrate composition or the carbohydrates themselves is in respect of the binding of the erythropoietin to receptors - in the case of erythropoietin, for example, to receptors in the liver?---For being taken out of the circulation.

Yes. What they go to is the amount of time that the erythropoietin can be maintained in the circulation in the body?---What is your question?

That the carbohydrate structures relate to the amount of time that the erythropoietin can stay in circulation?---That's correct.

They do not themselves affect the way in which the erythropoietin acts in erythropoiesis?---This is not correct.

You will agree that the conclusion in the literature is that the carbohydrates go to the clearance times of the protein?---This is clear, but not only.

You would agree that the role of oligosaccharides is primarily in the clearance rate from the circulation?---Yes. But that is not the sole reason.

You would agree, would you not, in the literature that you have annexed to your affidavits, the relevance given to the oligosaccharides are that they relate to the clearance times for the protein?---I don't know what you mean with this question now.

You would agree, would you not, that the references that you have annexed to your affidavit, when they talk about the oligosaccharides of erythropoietin, relate them to the clearance time of the protein in the circulation?---I do not remember that I have attached a reference which is precisely and exclusively dealing with this point, clearance rate. I have attached - if I can continue one sentence. I have attached a few references which deal with the biological activity of erythropoietin in connection to the carbohydrate structure.

You would agree, would you not, for example, that differences in sialic acid are specifically linked to clearance rates in vivo?---I agree.

You would agree with me, would you not, that the documents that you have annexed at AGH 5, 6 and 7 were published in 1990, 1993 and 1995?---This is 1993 and - - -

1990, 1993 and 1995?---Correct.

These papers discuss how glycoproteins can be modified after their synthesis and secretion from the cell?---I have to check them again, excuse me.

Please do?---I think number 5 is something different.

Number 5 relates to - it is not a paper on erythropoietin, is it?---No, it is an interferon gamma and it has not been - this is not about manipulation of the carbohydrate part F that has been made.

Is that a paper that observes prolonged exposure of cell culture conditions on glycoproteins?---Yes.

Is that after it has left the cell?---No. It could be also - there are various factors. The cell culture, if you keep the cell culture for a long time in culture, it can change the carbohydrate. It could be also that the carbohydrates of glycoproteins being already excreted and being in the medium be modified, it could be both.

But it is about interferon?---It is about interferon, correct.

I think I asked you - none of those three papers concern erythropoietin?---None of them. The second one concerns IGM, it's an antibody; highly glycosylated antibody.

And the third one?---The third one also does not include erythropoietin.

AGH 8 was published in 1989?---'89, correct.

And it is about tissue plasminogen activator?---That's correct.

You would agree, wouldn't you, that when you purify a glycoprotein on a column, it's normal to monitor purification by biological activity?---Yes, that's normal.

Then you just pick the fraction with the highest activity, if that's what you are looking for?---If this is what you are looking for.

Exhibits 9 and 10 are papers that were published prior to 1985, aren't they?---Yes.

And both of those papers relate to the effect on in vivo activity when sialic residues are removed?---That's correct.

And the removal of sialic residues which negatively affects the in vivo biological activity of EPO correlates with its rapid clearance from the circulation by interaction with receptors in the liver; do you agree with that?---This is correct, yes.

AGH 11, 12 and 13 were all published well after 1985?---Yes.

You would agree that in those papers the authors took deliberate steps in order to alter the carbohydrate residues?---Not in all of them.

Would you agree that in one of those cases, the authors deliberately replaced the three residues which were responsible for the attachment of the N-link carbohydrates with an amino acid which was known not to glycosylate?---Yes, because they were studying the effect of glycosylation, the amount of carbohydrates.

In another case that you have cited here, the authors deliberately used a specific CHO cell mutant, and that is in 12 and 13?---12, 13, they used a mutant which has a defect in the glycosylation. It is a mutant which produces different carbohydrate structures, shorter carbohydrate structures. They deliberately used this mutant to study the effect of this short carbohydrate structure on the activity.

In fact, in order to produce a mutant CHO cell without O-link glycosylation, Genetics Institute, in one of those papers, had deliberately to omit Gal and GalNAc from the growth medium?---I didn't get your question. Could you repeat it.

I will start it again. You would agree that in the GI paper, they had to deliberately omit Gal and GalNAc from the growth medium in order to produce the mutant CHO cell without O-link glycosylation?---No, I think this is not correct. You are referring to 13, that is what you are referring to as the GI paper?

Yes?---To make this clear.

It is not 13, I withdraw that. That is not a GI paper?---It's a GI paper.

I am looking at the wrong one, sorry. 13 is the GI paper?---Mm'hm.

Would you agree that what was done there was to deliberately omit galactose and n-acetylgalactosamine from the growth medium?---I don't understand what you mean with "deliberately omit" in this context.

To grow the cells in the absence of those two substances?---They did this, because otherwise you would not get the effect of this mutant.

And they also showed that a simple addition of those two products or compounds cured all of the defects?---That's correct. That lies in the nature of this mutation.

Was there anything in the Kirin-Amgen specification that told you, for example, that nutrients were deliberately withheld?---No, not that I can think of. But this is a special case, you know.

In paragraph 5.4 of your affidavit, you asserted that there may be - - -?---Are you talking about my first affidavit?

Yes?---Okay.

You asserted there may have been, during example 10, random insertions of transfected DNA into the genome of the cell and that such random insertions may have altered one or more of the enzymes involved in glycosylation, which may in turn have resulted in an altered ability to glycosylate?---Yes, that is what I have written.

Do you support that with a single publication?---I have not supported it with a single publication.

Are you aware that in GI patents there is routinely a recommendation of the use of CHO cells for high-level expression?---Yes.

And there is no mention made in those descriptions or any warning made that there might be incorrect splicing or improper glycosylation?---Not that I am aware of. I would like to add here something.

I just asked you the question, Dr Haselbeck?---That's it.

Dr Haselbeck, in saying in that paragraph that there may be random insertions, that such random insertion may have altered one or more of the enzymes involved and that that may have altered an inability to glycosylate, is simply pure cumulative speculation?---This is speculation, but this whole affidavit was written to explain an unusual carbohydrate composition and this is one of the possibilities, that by inserting DNA randomly into the genome and especially when you insert genomic DNA, which is very big, and you use this kind of construction with a DFHR minus mutant and you force the cell to integrate many, many copies of this genomic DNA, this huge piece of DNA into the genome randomly, and I would like to point out to you that about 100 to 500 copies of this genomic DNA are incorporated randomly into the genome. It can happen that you destroy other genes which are used for the glycosylation machinery within the cell.

So each of these theoretical possibilities would have to occur together or cumulatively for there to be an explanation of what you say are correct data?---This is just one explanation. There can be many - - -

Could you answer the question, maybe I didn't make it clear. In that example, do you agree that each of those things, those speculative things, would have had to have happened cumulatively to provide a possible explanation for what you maintain are correct data?---No, not all of them. It could be just one or two. I am not saying all of them have to occur in a cumulative manner.

You say there would have had to have been first a random insertion?---Yes.

And that that random insertion may have altered one of the enzymes involved in glycosylation and that that alteration may have resulted in an altered ability to glycosylate. So each of those theoretical possibilities would all have had to have occurred in order to explain the unusual or incorrect glycosylation data?---Yes. If you are referring to - I misunderstood the first question. If you are referring to this event, they have to occur, but not necessarily you have to have an insertion into a gene which is directly involved in the carbohydrate. It could be other genes. It could be a little bit different.

In that example that I have just taken you to, that you referred to there, each of those would have had to have occurred cumulatively?---Yes, but this is what occurs in the cell. The cell incorporates DNA randomly, so there are two of these three things you mentioned do occur; otherwise you would not get a recombinant cell line, a stably transfected recombinant cell line which produces erythropoietin. Only the third of my assumption, if it hits a gene which is responsible or involved in the carbohydrate metabolism, then you would get altered carbohydrate structure. But the other two do occur automatically.

It would have to occur to a sufficient number of cells across a mixed population of cells, this random event, in order for the result that you contend for to be manifest?---It's conceivable that if it occurs only in a few cells and by your selection process later on you pick out this one or these few cells, that it could be sufficient.

If it occurs across enough cells, if the effect of it has a bad effect on glycosylation, if you happen to pick out that cell, and if all of those things happen, you say theoretically it is possible that that could explain the glycosylation data?---That is what I am saying.

Isn't a more simple and obvious explanation that something went wrong with the analysis and that the data are wrong?---This would be a simple explanation if I would have been given the repetition of the analysis which would have shown me different numbers. All I have seen is a repetition of the analysis which have shown me the exact same numbers. So from this, I cannot conclude that a simple analytical error was the basis for this being put into the specification.

So you reject the simple explanation that something went wrong with the analysis, sitting here today and bearing in mind all of the data that you now know, you reject that simple explanation and prefer the theoretical possibility that all of those sorts of events occurred across a mixed population of cells and they happened to be chosen and that that provides a better explanation; is that what you're saying?---No, this is not what I am saying. I do not reject the simple explanation, but in the context of this patent specification, I would be confirmed that this data have been reproduced and verified. That's why I would not simply think it was just a pure analytical error, because something like this you would not put into a patent specification and you would not draw a claim on, based on this differences.

Where is the evidence that these incorrect data were repeated?---Evidence is in laboratory notebooks of Dr Yu and Dr Lin.

That it was repeated?---That it was repeated, that is what I said.

Can you please take me to the evidence that you say reports the fact that these results were done more than once?---Yes.

Where are they?---That's AU - I don't know the number exactly. Can I go to my table and get this? There are laboratory notebooks that have been deposited here. I have the numbers, we can look at those. It will tell you that the sample, two samples, have been analysed and the analysis data of the second sample have been put into the patent. That means they have been put into the patent only after they have repeated.

When you say "repeated", are you saying that each sample was analysed more than once?---No, I am not saying this. Two different samples have been analysed and each sample has been analysed, in one case three times, and in the other case I believe five times.

MR CAINE: Your Honour, there is not much point in speculating about this. The witness has given an answer and he says he can explain it if he is allowed to go to the notebooks which were discovered by Amgin from Dr Lin and Dr Yu. In my submission, he should be allowed to explain to the court what he has just said.

HIS HONOUR: Are the books here?

DR BENNETT: I don't know, your Honour.

MR CAINE: I don't have all of the books, your Honour, but I believe in his notes he has a reference to the page numbers in the books and he can at least be more specific about the point that he is seeking to make.

HIS HONOUR: He has been challenged on something, Dr Bennett.

DR BENNETT: Perhaps I can ask one question before and I am happy to see them.

Dr Haselbeck, when you say that they were repeated, when the result was repeated, the result that was obtained was different to the first one, wasn't it?---It was not different. The ratio which was very close to the first one. The ratio hexose to GlcNAc - - -

The results themselves were different?---They were certainly a little bit different. You will not get the same numbers. But the ratio and they are - they have put in the ratio hexose to GlcNAc and those are very similar.

MR CAINE: I am just concerned - it has been brought to my attention that one of the people in court on our side hasn't given a confidentiality undertaking. I didn't want any figures to be mentioned. One of the people instructing me has not given an undertaking as to confidence in relation to Dr Lin and Dr Yu's notebooks. I just rise now, your Honour, because I didn't want the witness to be asked a question that would lead him to reveal a figure that might be sensitive.

DR BENNETT: Perhaps we can have access to the data that Dr Haselbeck says he is relying upon to form his conclusion. We don't know which notebook pages he is referring to.

MR CAINE: Neither does he until he is permitted to go specifically to his notes to find out.

HIS HONOUR: Has he got his own notes here?

MR CAINE: I believe, your Honour, he probably has got some notes in court, I don't know, but he may be able to give a global explanation and then later on we can identify the pages to support that. I don't want it to be a test of his memory, I think that is unfair.

DR BENNETT: He has given a global explanation and he has referred to some pages of the notebook and we would like to know which pages he is relying upon.

HIS HONOUR: To your knowledge, Dr Haselbeck, are your notes, or the copy of Dr Yu's notebook, present in court?---Dr Yu and Dr Lin's, both sides.

You have access to that?---I have seen them. I have them and I have the number. It is AU 340 following. 340-388, I believe.

HIS HONOUR: Is that sufficient for your purposes?

WITNESS: That's the discovery numbers from Australia. I mean, I can - - -

DR BENNETT: We will check if that is right; if not, we will come back to you on that one, Dr Haselbeck. When did you first see these notebooks?---I have seen these notebooks in the Australian - I have seen these notebooks earlier, because I think they are publicly available out of the interference, the US interference.

You saw the notebooks that were in the interference; right?---I believe so.

Is this the same interference that EFF 23 refers to?---I believe - I was not involved, so I don't know exactly. I think there were different ones. If there were different ones, I cannot answer this question.

So you are relying upon data that was before the US Patent Office in the interference proceedings between Fritsch and Lin?---I do not know if they were before. I have no idea.

Are you saying those notebooks would have been available to Genetics Institute or Dr Fritsch, I should say, in the US interference matter?---I don't know.

The interference you are referring to was between Fritsch and Lin?---Yes.

And you are aware that after having examined those notebooks, GI's conclusion, and as Dr Fritsch said in relying upon himself and other GI scientists, were that the data reported by Dr Lin and Dr Yu with respect to the carbohydrate composition were manifestly invalid?

MR CAINE: That may not be a fair question. Dr Fritsch's evidence in cross-examination doesn't make clear what GI experts he spoke to and when and what documents he formed a view on.

DR BENNETT: I am happy to withdraw that part of it.

MR CAINE: It is unfair to put to this witness what - - -

HIS HONOUR: All right.

DR BENNETT: I am only going from what he heard Dr Fritsch say in the witness book. If my friend doesn't want to acknowledge that evidence, I'm fine.

MR CAINE: The evidence will speak for itself, your Honour. It was the question I was concerned about.

DR BENNETT: Are you aware that after looking at these notebooks that were apparently available in the interference decision that Dr Fritsch submitted formally to the Patent Office that the carbohydrate composition data were manifestly invalid?---This is what obviously Dr Fritsch did.

You would accept, would you not, Dr Haselbeck, that as at 1983 and 1985, it

was well known and accepted that CHO cells were particularly stable for the purpose of the expression of recombinant proteins, recombinant glycoproteins?---I don't know if this was so well established that they were stable.

Because you yourself were not working on that system at the time, were you?---I was not working on the system and not so much work was done in general on the recombinant expression.

But the work that was done, much of the work that was done, used CHO cells for expression?---For stable expression, that's right.

Dr Haselbeck, when you looked at the SDS page results, you saw a broad band or a smear?---Which SDS results are you referring to?

The earlier ones before the carbohydrates were removed?---Which - - -

I withdraw that. Generally, when you look at SDS page results with respect to glycoproteins from different host cells, the first thing you would see would be a broad band or a smear on the SDS page?---In case of heavily glycosylated protein, yes.

That would reflect the slight differences in molecular weight that you would expect to get because of the slight differences in carbohydrate structures that would be put on the proteins within the cells and between the cells?---That's correct.

By that, are we referring to the different branches of carbohydrate structures that can be put on depending on the time that an individual protein spends in the golgi apparatus or the endoplastic reticulum?---Yes, that's correct.

These expected slight differences in the branching of the carbohydrates is what can be referred to as microheterogeneity?---It's referred to as a heterogeneity, not microheterogeneity.

It is a different heterogeneity from the fact that across a population of CHO cells you will get heterogenous populations; it's a different heterogeneity to that?---It is a heterogeneity within one molecule actually.

And that sort of heterogeneity that we are talking about with respect to the carbohydrates is a normal occurrence in mammalian cell expression?---That's true.

Prior to 1985, how often had you yourself cultured CHO cells?---Never.

What is there in the specification that tells you that other than standard culture conditions were used?---Nothing. I believe it is mentioned they used standard culture conditions.

Is there anything in the specification that makes you disregard the express reference to standard culture conditions at pages 61 and 62?---No.

Taking you now to some of the other papers that you annex to your affidavit, AGH 16 and 17, these are papers which were published, were they not, in 1991 and 1989?---1991.

And 1989?---Yes.

You rely upon them to form conclusions in your affidavit, I think, at paragraph 3.17 of the second affidavit?---Yes.

Neither of those papers have as their subject matter recombinant erythropoietin?---No, but my affidavit was concerned about a possible explanation for unusual carbohydrate structure. It was not - - -

Do you agree that one of those papers doesn't relate to mammalian cells - AGH 16?---It relates to insect cells, I am aware of this.

In AGH 17, the authors concluded, did they not, that the oligosaccharide structure observed with tPA was dictated by the particular amino acid structure of that protein and was not a mere accidental activity of the CHO cells?---This is the general knowledge. This is known, the protein structure, the protein conformation dictates the carbohydrate structure, certainly the attachment of the carbohydrates at certain positions.

So that paper is not relating to accidental activity of CHO cells?---What do you mean with "accidental activity of CHO cells"?

The authors' conclusion was that the oligosaccharide structure that they observed was dictated by the amino acid structure of the protein?---I have included this reference - - -

Just answer the question. Is that what the authors concluded in this paper?---Yes. But I have included - - -

I didn't ask you why you included it, Dr Haselbeck, I asked you what they said in this paper?---But this is in reference to a certain paragraph in my affidavit.

I just asked you what the paper itself - what the authors said?---Okay, I answered this.

In that paper, the authors specifically distinguished, did they not, between the high mannose structure that they noted and other CHO cell expressed glycoproteins, including erythropoietin, which did not have high mannose structures?---Yes.

You rely also upon a paper at AGH 19. Do you have AGH 19?---Yes, I do.

You rely upon this paper to show that glucose can affect carbohydrate composition?---Glucose can affect carbohydrate composition, yes.

In this paper, what is reported there is that the cells were starved of glucose before an effect was obtained on carbohydrate composition?---Yes.

There is no suggestion in this paper, is there, that standard culture conditions would affect carbohydrate composition?---You can draw a conclusion from the glucose starvation to standard culture conditions. Can I explain this?

Are you saying that you can equate standard culture conditions with glucose starvation?---Standard culture conditions will contain glucose. The question is if you cultivate cells for a long time in a standard culture conditions and you do not add glucose, after a while you could get glucose starvation. That is what I mean.

If you use standard culture conditions and if you left the cells there too long and if there was insufficient glucose, then perhaps you might get an effect of deprivation of glucose; is that what you're saying?---Yes, and in the specification there is no mentioning that they have added glucose later on. They used standard culture conditions with glucose and left the culture for days.

Is there anything in the specification that says what was deliberately done was to - was there anything in the specification that says there was a deliberate glucose starvation step taken?---No, certainly not.

Are you aware at page 61 of the specification, it says that:

> *24 hours later the media were removed and replaced with ..... non-essential amino acids and L glutamine.*

?---Yes, but you have to continue - - -

Are you aware that it says that?---Yes, it says this, but it is just the first part.

This does tell you that steps were taken to ensure that a high glucose level was present?---At the beginning of the cultivation.

There is nothing in there, though, that says that, having been aware of the fact that the glucose was added, the work that subsequently was done was deliberately to starve the cells of glucose?---No.

Wouldn't you make the assumption, Dr Haselbeck, that if anyone wanted to produce a glycoprotein product in the way set out in the specification, they would not wish to starve the cells of glucose?---Normally, yes.

Going back to AGH 19, the authors concluded there, did they not, even where they specifically engineered cells by the environment, the effects were N-linked glycosylation and not O-linked glycosylation?---I think they were N-linked because they started mainly the N-link glycosylation. I am not aware that they specifically addressed the question of the O-link glycosylation in this publication.

At paragraph 5.19 of your affidavit, you refer to what you say are three reports of CHO cells which have been reported to produce a differently glycosylated EPO?---Yes.

HIS HONOUR: 5.19, did you say?

DR BENNETT: 5.19.

You would agree, would you not, that as at 1983 or 1985 you would not have been aware of any of those three reports?---Yes.

Two of the reports were published in 1989 and 1991?---I believe so, yes.

And they refer to specific and characterised mutations?---Which one are you referring to precisely now?

At paragraph 5.19, you are referring to two of them, being AGH 12 and AGH 13?---Let me just see that.

HIS HONOUR: This is in the first or second affidavit?

DR BENNETT: It's his second affidavit, but it goes back to AGH 12 and 13.

HIS HONOUR: What page of the court book?

DR BENNETT: AGH 12 is at 821, which is a paper that was published, was it not, in 1989, Dr Haselbeck?---Number 12, you're talking about. Yes, published in 1989.

And AGH 13, which is at page 826 of the court book, was published in 1991?---That's correct.

You would agree with me - I think you have already agreed with me - that that would mean that a person in 1983 or 1985 would not have been aware of the contents of those reports?---I agreed with you, yes.

Is it fair to say that each of those reports refer to specific and characterised mutations?---This is not correct. Report number 12 does not refer to a characterised mutation, as far as I understand it.

But it refers to a specific mutation that was being investigated there?---No, it

does not refer to a specific mutation, it just refers to a specific cell line being found throughout, I believe, the normal clonal selection process in the course of making EPO.

It was described as a unique cell line?---Correct.

You refer to what you say is a third report in paragraph 5.19, but you don't give a publication of that report?---No, I didn't. There is no publication.

Is that something that you know from Genetics Institute?---Yes.

And is that something that you know because of Boehringer's association with Genetics Institute?---Yes.

You say that that clone produced less highly sialated structures?---Yes.

That would affect the question of clearance?---Yes.

There is no suggestion, is there, that these three specifically obtained mutants just occurred because of the use of methotrexate procedures?---There is no specific mentioning of this, but all of them, I think, originate from methotrexate amplification.

Are you aware of the fact that DHFR gene amplification occurs by random duplication at one site, not by reinsertion of the DHFR at a new site?---I am not aware of this.

Do you deny that?---Yes.

You deny that?---Yes.

MR CAINE: There might be a difficulty about what the witness understands.

DR BENNETT: Sorry, tandem.

Are you aware that DHFR gene amplification occurs by tandem duplication at one site, not by reinsertion of the DHFR at a new site?---I am not aware of this. I am not really an expert in this field.

I see?---If it is only a tandem duplication, I am not positive about this.

Is that because you yourself are not really familiar with the way the DHFR gene amplification occurs?---I have never analysed, on the genomic level, the insertion of the DHFR gene.

So you would agree that it is not as though the chromosomes of the CHO cells are interrupted at hundreds of sites when a gene is amplified hundreds of times, are you?---I don't know exactly if this is on one site or how many sites. I would

expect this must be more sites than just one.

But you don't really understand how that works?---I understand it, but I just don't have the data here.

And you don't know?---I don't know, because I don't - I have never done it myself and I don't have the data here to extract this from.

N-acetylaglucosamine, or GalNAc, is the sugar that binds the O-link carbohydrate chain, is it not?---It is usually the first sugar which is linking other sugars to the amino acids.

You would agree that in 1983 it was difficult to detect the presence of O-linked carbohydrates?---It was difficult to detect.

You would agree that the enzyme that specifically removes that chain from the polypeptide backbone O-glycosidase, thus allowing for its detection, wasn't available until about 1985?---That's correct.

So you would accept that a failure in 1983 to detect GalNAc would not enable you to rule out O-linked glycosylation?---There are other ways to detect GalNAc than using this enzyme. I mean, GalNAc would be detected in the normal compositional analysis that has been carried out here.

So you don't agree that in 1983, the failure to detect GalNAc would not enable you to rule out O-linked glycosylation?---I didn't get this. Could you repeat that.

You agreed with me that it was difficult to detect the presence of O-linked carbohydrates in 1983?---Yes.

And knowing that it was difficult, would you agree that the fact that someone had not actually detected GalNAc would not necessarily enable you to rule out the possibility that there was O-linked glycosylation?---That's correct.

We talked earlier about possible contamination by the common contaminant hexose that might explain the erroneous hexose ratio. Do you recall that?---We were talking about this.

And you agreed that that was a possibility?---That's always a possibility.

You didn't mention that possibility, that always exists, in your affidavits, did you?---No, my affidavits were more concerned with the cell culture conditions which might influence the carbohydrate.

The only way to show that that contamination was in fact the problem would be to transport oneself back in time to 1983 and immediately check the columns that were used, wouldn't it?---Yes. That means repeat the experiment.

No. If subsequently you formed the view that there had been contamination by hexose, the only way to confirm that, if you only realised it at a later time, would be to transport yourself back to 1938 and check for contamination? ---Yes.

You would agree with me, wouldn't you, Dr Haselbeck, there is no report to this day of CHO cells spontaneously losing their ability to glycosylate?---The only report I know, and which is contained here, is not spontaneous, you're right, yes.

You would agree, wouldn't you, that carbohydrate composition data are not relevant to an assessment of tests conducted by radioimmunoassay?---I agree.

DR BENNETT: Your Honour, I am nearly finished with Dr Haselbeck, so we are moving along quite well. What we would like to do before he goes is to have a quick - I have a few questions left, but we would also like to have a chance to have a look at the notebook pages that he has referred to see if there are any further questions that arise in respect of those.

HIS HONOUR: Would you like me to stand the matter down for a short time?

DR BENNETT: Yes, and we will notify your Honour's associate. I am still hopeful we will finish by lunchtime.

ADJOURNED **[12.05 pm]**

RESUMED **[12.28 pm]**

DR BENNETT: Dr Haselbeck, you referred to some particular page of AU 0355 of the confidential exhibits taken from - - -?---355 is within those; not just 355.

You agree, don't you, that in each of those examples, on the face of the analytical results of the carbohydrates, what is shown is a mass imbalance, on the face of the document?---The mass imbalance - this what I have explained earlier that I was - - -

Can you just answer the question?

MR CAINE: This is a difficulty. If mass imbalance is a technical term of some sort, your Honour needs to hear why the witness says that.

HIS HONOUR: Feel free.

DR BENNETT: I will start again.

Do you agree that, on the face of the document itself, it shows that in respect of each of the examples with respect to the recombinant protein that was analysed, more mass came out in respect of carbohydrate than was put in?---There was put in only mass in terms of protein, not carbohydrate.

Do you accept that what was put in was mass in terms of glycoprotein?---In terms of protein. This is my belief.

That is your belief?---That is from measuring absorbance at 280.

You gave an explanation earlier that, in order to explain these data, you have assumed that Dr Lin's analysis was incorrect?---That's what I would have assumed, seeing those data.

And you assumed that in order to explain that the carbohydrate composition data were correct?---Yes.

You would agree with me, would you not, that if you have a contaminated sample that you are testing, no matter how often you test it, the contaminant, if it is one that you are measuring, would affect the results?---If you always test the same sample, yes.

And you would also agree with me, would you not, that if you had a contaminated column and put a series of (indistinct) through that column, using the same column, that the contaminant would affect the results?---I don't understand precisely what you are asking.

If you have a contaminated column, a contaminant in your column?---What do you mean with a contaminated column?

A contaminant present within the column?---This would be washed out in a very short time, so I cannot think of a contaminated column which would contain this contamination throughout the purification.

Throughout analysis?---Purification, not analysis. The column is not analysed.

If you were using a column for gas liquid chromatography and there was a contaminant in that column and you put, for example, one sample in there after the other, both of those samples would be affected, or the results the from each of those samples would be affected, by the contaminant in the column?---I would expect when you put various samples through the same column, like the gas capillary, if there would be a contaminant, the contaminant would be washed out and diluted. You could have a contamination in your first sample, maybe a little bit less in the next, but then it should decrease and there should be then no contamination after a few runs. Normally, standard runs will be performed on a capillary chromatography system to ensure that there is no contamination. And I would also think that somebody like Dr Yu, who was a carbohydrate person, he knew his machine and he knew how he had to perform

this type of analysis. Otherwise, Dr Lin would not have sent these precious samples to Dr Yu.

Are you assuming that Dr Yu himself performed these analyses?---I assume that Dr Yu or I assume that a technician in Dr Yu's laboratory would probably have performed the actual analysis under the supervision of Dr Yu.

You are aware, are you not, that the sample taken for the purposes of the analysis in example 10 was a heterogeneous population of CHO cells?---The sample was a purified recombinant protein, and not a population of cells.

No, but that protein was expressed from a heterogeneous population of CHO cells?---This is not precisely mentioned in the specification, but I would assume that that was the case.

And you are aware, are you not, that Dr Browne's evidence is that even today the recombinant EPO that is made by Amgen is produced by a cell line that was present in that population of heterogeneous CHO cells that was where the protein was expressed and taken from in example 10?---This is contained in Dr Browne's affidavit. I have seen this.

Even as at today, are you aware of any heterogeneous CHO cell population, any CHO cell line under any culture conditions or any mutant CHO cell line that has been reported to produce a hexose ratio of the order of greater than 15?---I am not aware of one, besides this one in the specification.

And you are aware that this has never been able to be repeated?---No, because it is deposited.

You are aware that there has never been any publication or any report of any of those sorts of matters that I put to you: a heterogeneous CHO cell population of any CHO cell line under any cell culture conditions or any mutant CHO cell ever been reported other than this result ever to show a hexose ratio of greater than 15?---That's correct.

DR BENNETT: Nothing further in cross-examination.

MR CAINE: I notice it is almost lunchtime. I wonder if I could have a few minutes to seek some instructions so that I can re-examine briefly.

HIS HONOUR: Do you want to re-examine after lunch?

MR CAINE: If that is convenient, to your Honour. I don't think I will be very long at all, it is just that I need to, for example, get the page of Dr Lin's notebook.

HIS HONOUR: All right, that is fine. Before we adjourn, Dr Bennett, it

might be useful if you could briefly recapitulate where the issues that Dr Haselbeck deals with fit into the structure of the case.

DR BENNETT: Now we are back to the same position that we were in before. It is our position that all of this material is irrelevant, for a number of reasons. First, we say that the carbohydrate composition data have no effect - the fact they are incorrect have no effect whatsoever.

HIS HONOUR: Before you get to that, as you understand it, how does the applicant put this evidence?

DR BENNETT: Our understanding is that the applicant is some way trying to say that we should somehow be limited in our claims only to a protein that has this particular carbohydrate composition characteristic.

HIS HONOUR: I notice it is related to claim 39, isn't it?

DR BENNETT: Yes. I think they are saying that everything should be limited to that, your Honour. They are trying to say, "You made this mistake and that must be all you got and that is all you can have". That is our understanding of what they are saying. Certainly claim 39 is the only claim that refers to carbohydrate composition at all. But all that is says is that you have an average carbohydrate composition which differs from that of naturally-occurring human EPO, and that is reflected clearly in the SDS page results. It is not a question of the exact carbohydrate composition, but simply, as we know, as was shown, that the glycosylation pattern in the COS and CHO cells was different to the glycosylation pattern of urinary naturally-occurring EPO.

HIS HONOUR: The way you put is that it is an essential element of claim 39 that it is different.

DR BENNETT: Simply that it be different.

HIS HONOUR: Is that the same thing as saying "not necessarily the same as"?

DR BENNETT: That is saying that it has to be different.

HIS HONOUR: It has to be different?

DR BENNETT: Yes.

DR BENNETT: Are we saying it is an essential integer of that particular claim that the average carbohydrate composition is in some way different, in any way different - - -

HIS HONOUR: It has to be different. And if it happens to be the same, that is not the plaintiff's claim.

DR BENNETT: It is not part of claim 39. I don't know to what extent there is an issue as to what is the meaning of "average carbohydrate composition". We say that reflects the sort of heterogeneity that this witness has also agreed to, and it is reflected in the evidence: that within a population of CHO cells or COS cells, you will get, across any difference in cells or within cells, slightly different sugars put on the protein. So what we are talking about, and what anyone would understand by that term, is that average carbohydrate composition means taking into account the fact that you might have what is called ailquots tetra antenarry, four branches instead of two branches, and that depends on how long the sugar stays in the - - -

HIS HONOUR: It's like saying some people have dark hair and some people have red hair.

DR BENNETT: Lighter brown or darker brown, or longer or shorter hair in this case. It is probably more like longer or shorter hair, and across the population if you can establish that there is a difference which is reflected in the molecular weight, because each of these sugars has a slightly different molecular weight, then you are entitled to the population of people, irrespective of their hair length, because that is what you have disclosed. It is also what naturally arises when you take the sugars that are produced in CHO cells or COS cells or any other sort of closed cell, you get a range of people, different hair lengths.

What claim 39 is aiming to do is simply to give it as an extra characteristic or an extra part of what is claimed in claim 39, a product that is different to the natural-occurring product. While it is easy to talk about average carbohydrate composition, that is reflected in molecular weight differences, for example, and that is what is shown on page 64. In fact, it was shown in different stages. Your Honour will recall that page 64 says you start off with CHO, COS and urinary and they have slightly different molecular weights, because COS and CHO and urinary glycoslate differently. You use an enzyme that takes off the sialic acid residues and you have COS and CHO then having similar molecular weights but still different from urinary. You take off all of the carbohydrates completely and you get equivalent molecular weights.

So the differences that you see are between human and recombinant, when you have sugars on them, and again you see slight differences in molecular weight when you have different expression in CHO cells, because the machinery of glycosylation is peculiar, how they glycosylate is different with every host cell, but it is part of the naturally-occurring thing of what they did and everyone would anticipate that. But you would expect glycosylation in the COS cell. The natural sort of glycosylation that a population of COS cells give you would be different from the naturally-occurring glycosylation that CHO cells would give you, and that's reflected in, or able to be estimated by, the molecular weight. We say that the carbohydrate composition data was just extra data that were put in for the heck of it really because it was - - -