COMMISSION OF INQUIRY
ON HORMONE RECEPTOR TESTING

BEFORE THE HONOURABLE JUSTICE CAMERON - COMMISSIONER

June 27, 2008

Appearances:

Bernard Coffey, Q.C. . . . . Commission Co-counsel
Sandra Chaytor, Q.C. . . . . Commission Co-counsel

Rolf Pritchard/Jackie Brazil . . . . Her Majesty in Right of NL

Peter Browne/Jane Hennebury . . . . . Doctors Kara Laing et al

Daniel Simmons . . . . . Eastern Regional Integrated
. . . . . Health Authority

Ches Crosbie, Q.C. . . . . Members of the Breast Cancer
. . . . . Testing Class Action
Mark Pike . . . . . NL Medical Association
Jennifer Newbury . . . . . Canadian Cancer Society (NL Division)
David Eaton, Q.C.. . . . Central, Western and Labrador-Grenfell
Regional Integrated Health Authorities
Simon Clements . . Drs. O'Malley, Pritzker, Wegrynowski & Mullen

LIST OF EXHIBITS

TABLE OF CONTENTS

COMMISSIONER:
Q. Please be seated. Mr. Coffey.
DR. BRENDAN MULLEN, EXAMINATION BY BERNARD COFFEY, Q.C.
COFFEY, Q.C.:
Q. Thank you, Commissioner. Commissioner, yesterday when we left off, I had just shown, I had the Registrar show the--Dr. Mullen Exhibit P-1840. But before we actually delve into that, because there are certain terms that are used in it, words or terms used, there is a PowerPoint presentation, that short one that Dr. Mullen has prepared, it's Exhibit P-1839.
COMMISSIONER:
Q. All right, then.
COFFEY, Q.C.:
Q. And I'm going to ask Dr. Mullen to take us through it, and provide some commentary upon it and to bring, you know, certain aspects of what's depicted in the screen to your attention, you know, elaborate upon them, okay.
COMMISSIONER:
Q. Okay.
COFFEY, Q.C.:

Page 5

Q. Go ahead, Doctor.
DR. MULLEN:
A. As Mr. Coffey mentioned, I thought in preparation for appearing before the council, some of the terms I use are quite technical and I thought a visual presentation might help.
COMMISSIONER:
Q. Um-hm.
DR. MULLEN:
A. This is not intended to be pathology 101 or complete pathology, it's very, very basic. And if I'm using terms that you don't understand, anyone doesn't understand, please interrupt and I'll try to be--explain as well as I can. What--yesterday when I was referring to the, once the specimen is removed from the patient and prior to its arrival in the pathology department, then handling has to be extremely standardized and meticulous. Once it arrives in the pathology department, we immediately section it. And when I talk about sectioning, I mean, it's--let me just--we make--oops, sorry. We make cuts in the specimen and these, by and large, are about

Page 6

one centimetre, 1.5 centimetres in width. And we cut right through the specimen, we leave them adherent to the back. This is to allow the formalin to penetrate. Formalin is the fixative which cross links proteins, and it has a penetration rate of one millimetre per hour. And I'll show you a cross section and what the implication of that is. And here you can see the specimen here, five centimetres long here. So this specimen would probably be 15 to 20 centimetres in this diameter, probably the same int hat diameter and eight or ten centimetres in thickness. So that would be, for formalin to penetrate the maximum would be if we divided in half would take 40, basically take 40 hours and by the time the formalin penetrated the centre portion of the specimen it would be autolyzed.
COFFEY, Q.C.:
Q. And that, I take it, Doctor, would be if there were no cuts made?
DR. MULLEN:
A. No cuts, yes. If we're--now, let's go back to my peach yesterday. So if I have my peach and I throw it in the formalin, the peach would

Page 7

probably be four centimetres, so for it to penetrate would take two centimetres or 20 hours for it to meet from both sides, a minimum of 20 hours. And while that's occuring the centre of the tissue is, because of the lack of blood supply, enzymatic processes would start to deteriorate. Now, we then place paper towels, these are what we call wicks, paper towels between the slices partly to keep the slices apart and partly to allow the formalin to be drawn into the specimen and it's placed in a volume of formalin that's anywhere from 15 to 20 times the volume of the specimen. We're limited because our containers are about four litres, but we try to--we maximize the fixative to the formalin. The formalin is very cheap, it's about $13 or $14 for 20 litres, so it's the most inexpensive product we have in our laboratory. Now, this is a--this is not from the original breast that I've showed you. This is a cross section of a, what we call a lumpectomy. The previous specimen is what would have been a mastectomy. And as you can see, let's see, the outside of the specimen

Page 8

and then this is the tumor. Now, this is a fresh specimen, it hasn't been fixed in formalin. So and here we have the ruler, so depending on the maximum diameter here, it would be probably about a centimetre to the edge of the tumor, probably a centimetre and a half to the tumor, so that's 15 hours before the formalin penetrates. And if you haven't made a cut in the specimen, the fixation, it would take 15 hours and -
COFFEY, Q.C.:
Q. I take it, Doctor, there's been no cut here, from the outside in it would take -
DR. MULLEN:
A. Yes, sorry, if it were intact and you hadn't made the--basically if you had the peach without cuts, it would take probably 15 hours to fix this specimen. And fat is very poor in fixing. So it's imperative that the specimen be handled properly. The minute it's removed from the patient, it has to be placed in a refrigerator, formalin in a refrigerator and then transported to the laboratory as quickly as possible, because it's the laboratory's responsibility to process the specimen

Page 9

properly to make these cuts, to allow the fixative to penetrate, to put in the paper towel. So that's the imperative of the laboratory. So it's in collaboration with nursing, the porter system and the laboratory we have the proper handling of the specimen. Now, the next, I'm going to take you through a series of slides. On the left-hand side will be examples of the specimens that I will referring--or the cases that I will be referring to today in the review of the original material. In preparation for my visit here, just before I sent the slides back, so that would be the end of April, I believe, somewhere around then, I had a few breast cases from the Sinai, so these are not selected, this is not selected the best I can do, this is what happened to arrive on my desk that day. So basically what I'm going to show you is the differences in proper fixation, handling, fixation and processing from what I consider acceptable on the right-hand side, which is the Sinai case and on the left-hand side, a compilation of cases from the Newfoundland material that I reviewed. The

Page 10

original -

COFFEY, Q.C.:

Q. The slide, what we will be--later on what we will be in the morning referring to a slide review.

DR. MULLEN:

A. Yes. These are not slides that were restained at the Sinai, these are the slides that were processed, stained in Newfoundland and then referred to me to review, okay. So basically here we have, this is the--on the right-hand side, this would be a breast cancer and the adjacent tissue would have fat and fibre connective tissue and benign ducts. These spaces are fat. On this side, this is a, the section from Newfoundland, and here where we have fat and--it's a complete section. Here we have large, large gaps of the specimen that aren't on the slide, so when the--this was improperly fixed or processed or fixed and processed and when they were cutting, these parts dropped out, they weren't able to adhere to the slide. So one of the difficulties in assessing unfixed, unprocessed or improperly fixed, improperly processed material is the

Page 11

lack of a complete section. So you're not sure if you are getting the complete section, so you may have tumor, you may not have tumor, you may have portions of the tumor. Now, when I'm doing my--I referred to yesterday, when I'm looking for benign ductal epithelium, I scan the slide looking for benign ducts, so when I go on to my estrogen and/or progesterone receptor slides, I'll have some indication where to look on the slide. And I also want to know where the tumor is because you'll see as we go through the Newfoundland cases, I have to visualize where on the slide I should be looking. Now, these are--this is now the exploding slide issue or the exploding specimen issue. These are estrogen receptor stained specimens. This is the same slide that I had from the Sinai, so this is the tumor area. And you can see at this power, it's staining brown and you see the complete section, although it's an outline, you can still see the complete section. On this slide you have large, large gaps, as we go through here, and folds here, so whatever tumor was there in this area has dropped out. And so

Page 12

what's left there to assess is very limited and it may not be representative of the entire tumor. I have no guarantee that what's present and what drops out are equivalent. And this is another example, this is even worse, this is the same section that I showed earlier and -

COFFEY, Q.C.:

Q. And on the right is from Mount Sinai?

DR. MULLEN:

A. Yes, Mount Sinai. And here -

COFFEY, Q.C.:

Q. It's Mount Sinai's own produced -

DR. MULLEN:

A. Yes. This is a case -

COFFEY, Q.C.:

Q. - specimen and slide?

DR. MULLEN:

A. - this is in-house case stained with estrogen receptor. The difference here, if I go back to the--this is a hematoxylin and eosin, it's pink and blue, the standard. Pick is the cytoplasm, blue are the nuclei. Here the brown is the ER stain and we only use a counter stain, so you don't see the same

Page 13

detail. It's not as though my--it's over exposed. It's a--this is the type of specimen we look at. And you can see these large, large gaps even worse that then--oh, no, that's the same one. Here, I mean, it's basically you throw something at a wall and hope something sticks, that's what it is. Large, large areas missing, just--and other areas where it's folded over. Now, I'm going to take you through some hematoxylin and eosin slides, these are microscopic, there'll be a low power, a high power and then we'll do the estrogen receptor and progesterone receptor. On the right-hand side we have the Sinai again. This is the histology of the slide I showed earlier. And this is an example of a case from Newfoundland. So if you look, here we have, this is tumor in this area and these are benign ductal epithelium. This is what I'm always looking for when I assess the slide at low--to see do I have tumor, do I have benign ductal epithelium. And then so I can then go on when I do my estrogen, progesterone receptor to look at those areas. And here, so we'll see the slightly higher power. In this

Page 14

area we have some residual epithelial cells, but the majority of the tumor I have here is dicrotic, and at a higher power I'll tell you what those features are. Basically I'm seeing amorphous blob like material. I don't see the distinct outlines of cells. At a higher power you can see benign ductal epithelium and the tumor. And here you can see some residual cells; there is some staining blue. But these are what I'm referring to in the report as hollow nuclei. And basically what happens is as the cell dies or--and starts to autolyse, the chromatin, which is basically nuclear substance, starts to leach out and, drop out, and you have nothing, you have basically an empty space. And the idea when one stains for estrogen and progesterone receptor is to stain the nuclear substance for the protein, so if you have nothing left in the nucleus, you wouldn't be able to stain or if it's markedly decreased, the intensity of the stain will be almost nil. And I'll show you that as we go-- okay. Now, this is an estrogen stain, again, of the same case from the Sinai. This is a low power. And a case from the Newfoundland

Page 15

material. It's not--doesn't--it's not the same as the exploding slides. Excuse me. Now, this is an example of a positive estrogen receptor. You can see the--I won't give you why they--these are malignant glands and the cells are staining strongly. You can see strong intensity here, variable intensity but almost, I would say, here probably 90 percent of the cells are staining. And here what I'm always looking for, what I keep referring to as the internal control, I'm looking at the benign ductal epithelium and checking to make sure that the specimen worked--specimen stained. So you can see--oops, oh, there it is. You can see in the benign ductal epithelium the cell is staining almost as intensely as that one. Here's one that's staining almost as intensely as that one. And if you recall yesterday I mentioned that in postmenopausal about 90 percent and in premenopausal 80 percent of women will have benign ductal epithelium that stains with estrogen, progesterone receptors, so that's my built-in standard. It's not 100 percent, but it's what I can use. Now, this is an example

Page 16

of Newfoundland's case material. Here we have some benign epithelium and here we have tumor. And you can see the difference in intensity, you can--if you squint and use your imagination, you can see a faint brown blush in the tumor cells. And here you can see, this is the internal control, and when I--the external control probably stained a little stronger than this, but this is what I used as my baseline. If these cells stained and this was the strong intensity, then I would accept these as staining positive. And if we look at a higher power, you can see, again, the benign ductal epithelium staining and then the tumor staining. And here you can see there's a faint brown blush, but the majority of the nucleus, as you can see, is gone, so there's nothing there in the majority of these cells to allow the protein--or the antibody to stick to the protein. But there is a brown blush in these cells. Unfortunately, I don't have a benign epithelium in this field. So that's-- so yesterday when I was--when I have a breast case and I'm ordering in-house, so something that's done at the Sinai, I can choose the

Page 17

block that includes benign ductal epithelium so I'll have that internal control as a check in addition to the external control. And if we go back here, this is the difference between a pathologist knowing that that this is a good peach and that's a bad peach, that you really look at it and you know there's something wrong. Something's got to be in your fixation processing that, specimen handling, fixation and processing, that caused this artifact or this abnormality, okay. So I've covered the concept of fixation processing, the need for slicing, the formalin penetration, the rate and so why we do that fixation rate. I covered the presence of benign ductal epithelium ideally within the tumor but adjacent to is not bad, but hopefully on the slide. And then the artifacts that I'm referring to, the hollow nuclei and the exploding specimens. Is there any other that -

COFFEY, Q.C.:

Q. Doctor--sorry, go ahead.

COMMISSIONER:

Q. Sorry. No, you mentioned the intensity of the

Page 18

staining?

DR. MULLEN:

A. Yes. That -

COMMISSIONER:

Q. How important is that?

DR. MULLEN:

A. Well, that's usually a function of the amount of protein.

COMMISSIONER:

Q. u

DR. MULLEN:

A. But the studies have found that the intensity is graded as zero is absent, one for weak, two for moderate, three for strong, that the intensity is not as important as the percentage.

COMMISSIONER:

Q. Okay.

DR. MULLEN:

A. So as long as you have some, that's adequate. And I think Dr. O'Malley would have taken you through Allred scores -

COMMISSIONER:

Q. Yes, she did.

DR. MULLEN:

Page 19

A. That would be--and I think she indicated originally we were looking at the combination of the two, but now the more important is the percentage.

COMMISSIONER:

Q. Okay.

COFFEY, Q.C.:

Q. Doctor, the slides that we've--or the photographic images of the slides from Newfoundland that you were asked to look at during the slide review in 2008 -

DR. MULLEN:

A. This is the -

COFFEY, Q.C.:

Q. You've had them up there on the screen. This is some of those slides.

DR. MULLEN:

A. Yes, yes, these are representative.

COFFEY, Q.C.:

Q. Sure.

DR. MULLEN:

A. This was--when I say representative, the boxes were ready to go back, and to grab a slide. I think I'd better have some example that--because using terms that people aren't

Page 20

familiar with.

COFFEY, Q.C.:

Q. If possible, it's useful to have them visualized.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Doctor, those sorts of artifacts, as you referred to them, depicted on these slides, in your view, should they have been apparent to any pathologist who looked at those?

DR. MULLEN:

A. Yes. Yes, they should.

COFFEY, Q.C.:

Q. And I appreciate they weren't originally your cases, but if you, in your experience, had come across such slides in the past, you know, and being asked to interpret them, what, if anything, would you do?

DR. MULLEN:

A. Well, I think, as I graphically said yesterday, one I would think about. One I might let go. Two, umph, and then three, excuse the expression, and I continued on. We would immediately go back to--well, I would

Page 21

start with the path assistants, the people who actually gross the--when I say gross, people who actually accession the specimen and section it and fix it. Was there something wrong? When was this removed from the operating room? What did we do wrong? Why is this specimen not fixed? And then, if everything were fine there, I would then go on to the histology lab. Is there something wrong with our processor? Again, the processor is the machine that takes the fixed specimen and makes a paraffin block of it, that process. Is there something wrong there? And then if not, if neither of those, then we go back to was there a delay--those are easy to do because they're in house and they're very close to me.

The next is if those two are correct, then we go to the operating room and what time was it removed? Was it left in the operating room or was it immediately brought to the histology area and put in the fridge in formalin? Was there some difference? Did we have a new nurse? Did we have a new porter? What caused this abnormality? So that would

Page 22

be the basic process.

So the artifacts that I'm showing here are not immunohistochemistry artifacts. These are artifacts or abnormalities, to use a different term, that are caused between the time the specimen is removed from the patient to the time it is put in--a paraffin block is removed--sorry, paraffin block is prepared.

COFFEY, Q.C.:

Q. Now Doctor, could you describe for the Commissioner, please, what process, physical and mental process you go through in a case, for example, an in-house case at Mount Sinai from the perspective of you've ordered an ER and PR and I gather HER2/neu has been ordered for a particular patient, and you ordered the ER slide, the PR slide, I gather and H & E slide would show up and you've described how you would pick a particular block to do this. Perhaps you could just take us through, all the way from what you're--all the way including looking down through the microscope, as to what you're looking for.

DR. MULLEN:

A. All right. So the first--so step through, and

Page 23

stay on the right-hand side. This is a low power, this would be about a ten power magnification, so the actual is about a hundred of the original. I would examine the slide to make sure, before I order my--to order my ER and PR, I would look at the tumor, decide what type of tumor it was and do all the--for the synoptic reporting for the basic tumor. I would look to select the block for the ER/PR and HER2, I would look, not so much for the HER2, but for the ER and PR, look to find the presence of benign ductal epithelium, ideally as I said, within the tumor, but closely adjacent to the tumor. I mean, it's fine if I have to say I have benign ductal epithelium on the surface, but if this specimen wasn't processed properly--oops, I've lost my pointer--wasn't processed properly, the ductal epithelium out here may react but it wouldn't react in there. I've tried to make sure that it's as close to, if not within the tumor. So that, I would order my ER/PR and HER2.

COFFEY, Q.C.:

Q. On that particular block?

Page 24

DR. MULLEN:

A. That block, and then, so I'd receive the slides. This would be a--I would look at it at low power, so basically I hold it up, see if there's any tumor, anything staining brown, then I'd go to a--put it under my microscope at a low power, scan the slide to basically follow that visual path as we go across, to yes, I have tumor. Then yes, I have ductal epithelium. Yes, the tumor is stained. Yes, the ductal epithelium is stained. Or no, the tumor has not stained and the ductal epithelium has stained or no, no. So those three combinations. The yes, yes, fine. No, yes, fine. No, no, neither, then I have to stop and think. Is there something in our technical? Is there some--so then I would look at the external control and I would look at the next--usually I get more than one case a day. I would look at the next case before I reported that one to make sure that the stains had worked, the internal control on the next case.

So the two extremes are very easy. If there's no staining in this tumor, it's zero.

Page 25

If there is staining and it's almost every cell, I report it either as 95, because there's always one or two that aren't staining, or occasionally I would report it as 100. Then, the next--so it's not those two extremes, I then look--step across the slide with my microscope, and when I say "step across" I move it sequentially across looking at each field. Field is my field of view. And assessing the proportion of cells that are staining. So I get the numerator, what--so the numerator are those cells staining brown and the denominator is the tumor cell. So it's numerator over denominator, and ideally, those of you who want to quibble about mathematics, ideally we would have the same amount of tumor in each field. So I can then do the average of the average. But if I don't, then I have to do some slight mathematical calculations. So it's numerator, number of brown, over brown plus tumor cells that don't stain for each field, and I go across it sequentially. Some of--I mean, and then I derive my percentage and I would then enter it in the synoptic report, which we saw

Page 26

yesterday. Then I would repeat the process for PR and -

COFFEY, Q.C.:

Q. For the PR slide?

DR. MULLEN:

A. Yes, PR slides. So that same process, look, did it stain, did it not stain, the controls, the tumor, and then go the same and step across. And then I think the--then, and then, so that's the actual physical. Then I--the thought process going through, all right, so if this is a well differentiated tumor or if it's a lobular type or tubular type or a mucinous colloide and this didn't stain, I mean, if they're anomalies that don't fit what the literature is, then I would--even though it didn't stain, I'd think again and I might have it repeated. So if I'm expecting a lobular carcinoma, a well differentiated carcinoma to be positive and it's not positive or it's not staining, even though the internal control, I may have it repeated because it's not fitting my preconceived idea of what the result should be. Even though everything technically looks fine, biologically it's not

Page 27

fine and let's repeat it before we go out. So these are--lobular carcinomas are about, what, 90 percent positive, if not almost 100 percent positive. So if one of those turns out as being negative, alarm bells are going off. Let's go back and repeat. I mean, these are--the delay would be a day at most in reporting, but I think it's more important that we get the biology right before we report it.

COFFEY, Q.C.:

Q. Commissioner, you haven't intervened. Are you -

THE COMMISSIONER:

Q. I'm following so far.

COFFEY, Q.C.:

Q. Good, okay. I'll be relying upon you to intervene.

THE COMMISSIONER:

Q. I'm with you.

COFFEY, Q.C.:

Q. You haven't shown any reluctance in the past, so I do, in terms of that, just -

THE COMMISSIONER:

Q. Yes.

DR. MULLEN:

Page 28

A. This is pathology 101, so the most basic.

COFFEY, Q.C.:

Q. So Doctor -

THE COMMISSIONER:

Q. Basically, all the latter part was just your way of saying that you're not just looking to do a mathematical exercise. You are thinking about what it is you're looking at and what one should see?

DR. MULLEN:

A. Yes.

THE COMMISSIONER:

Q. And using that to make a determination as to whether or not this is a slide on which you are prepared to give your opinion?

DR. MULLEN:

A. Yes, that is correct.

THE COMMISSIONER:

Q. Okay.

DR. MULLEN:

A. If you look--I mean, I believe Dr. O'Malley would have talked about the percentages that are positive.

THE COMMISSIONER:

Q. Um-hm.

Page 29

DR. MULLEN:
A. You know, you can--I mean, any one slide can vary from what they expected. I mean, you know, we keep track of our statistics or I keep track of my statistics, what are positive, what are, you know, ER/PR positive, ER positive/PR negative, ER negative/PR positive and neg and negative, but you know, if I wait until I get a deviation from what the expected percentage is, and I'm not quite sure what deviation I would expect to trigger something, we trigger investigation based on each case. If there's something that doesn't fit, we then--we meaning myself and my colleagues and the technical staff, go and try to explain the abnormality or the deviation. I mean, that's not to say that you won't have a lobular that's negative, but you'd better make sure that you're happy it's--or that you're satisfied that all the technical, all the processing, and your interpretation are correct before you issue a negative report.
COFFEY, Q.C.:
Q. Doctor, if we could, please, if we could bring up, please, Exhibit P-1771? Now Doctor, we

Page 30

have heard references here from other witnesses from Mount Sinai to a form called a client satisfaction form or client satisfaction record.
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. That's correct?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. What is a client satisfaction record? What's the purpose of it and what's it used for?
DR. MULLEN:
A. Well, the client is me. The client is the pathologist. It's used for communication between the tech--and documentation between the immunohistopathology lab. We also have it in our other labs. It would just have a different title. It's to explain or to flag technical issues to explain the quality of the slide. If the quality is not up to our usual standard, if there's any deviation from the quality, I will get this slide and the technologist will attempt to explain why the

Page 31

slide is not up to our standards. And in this case, the surgical case number has been redacted, outside number, I'm not sure. It's 06124. It's from the submitting hospital, sometimes I don't have the submitting hospital. It's case number and then these are--since they're all St. Clare's Mercy, they haven't put my name here, and then the MLT comments, poorly preserved, and then the initials. So each technologist -
COFFEY, Q.C.:
Q. Is that pro, poorly preserved or -
DR. MULLEN:
A. Poorly processed, sorry. Poorly processed.
COFFEY, Q.C.:
Q. In that world, what does that mean, in your world?
DR. MULLEN:
A. That would have been either the fixation and/or processing that we cannot--once we have the block, so this is material that's been processed outside, fixed--removed, fixed, processed and a paraffin block prepared outside the hospital. So we use the term processed, fixed, whichever, I mean, almost

Page 32

interchangeably. We cannot tell which of the two or if either of the two or both of the processes were unsatisfactory. So basically, what we have is a block that we have difficulty making a slide of, and this would-- if you go back to my--if you remember my first H & E slide, we would end up with holes possibly, and then when we're doing the immunohistochemistry, because we do antigen retrieval as part of the standard ER and PR staining which requires heating in an acid, it would most likely explode.
COFFEY, Q.C.:
Q. If we could -
DR. MULLEN:
A. And then -
COFFEY, Q.C.:
Q. Go ahead, sir.
DR. MULLEN:
A. So we go, and that's for me to fill in, whether it--and then corrective action. Here, there's not much corrective action we can do, and then I would sign it.
COFFEY, Q.C.:
Q. Doctor, here, on page two of the exhibit, this

Page 33

is just another case.
DR. MULLEN:
A. Yeah.
COFFEY, Q.C.:
Q. And the date request received, March 7th '06, and date slides completed, March 8th '06, and it's written here "tissue lifted from the slides in immunostain. If needs to be repeated, please let us know." So I take it this is something that comes to yourself?
DR. MULLEN:
A. Yes. So this would be--I can't speak to the specific case, but reading what they're saying, this would be the issue of the exploding slide or lifting and parts had fallen off, and the question they're asking me is "do you feel that there is enough identifiable tumor present to render an interpretation?" and that would be the--this would be the immunostains so it'd be ER/PR, either the ER, PR or both.
COFFEY, Q.C.:
Q. And here, go on to page three of the exhibit, there's again an outside case number. The pathologist is indicated to be yourself. The

Page 34

date is April 6th, 2006, and under the comment there's "Fatty tissue received. Unable to cut sections due to unprocessed tissue. Tried to cut at 5 -
DR. MULLEN:
A. At 5 and 6 microns.
COFFEY, Q.C.:
Q. - and 6 microns. Not possible" and the TW?
DR. MULLEN:
A. That's Trish.
COFFEY, Q.C.:
Q. Trish Wegrynowski. So this would communicate what to yourself, what sort of -
DR. MULLEN:
A. That we'd have to ask for another block. They can't get a section. This is not one of the issues of being able to get a section and then doing our little trick of putting it in--I don't know if she explained the issue of putting it in alcohol, floating it in alcohol. Usually when we cut--when we, the technologists cut a section, it floats in water and then they put it on the slide. If they're having difficulty cutting the section or it's starting to break up as they're

Page 35

cutting it, they have a little trick, some of them have a little trick where they put some alcohol, it doesn't really matter what the dilution is, some alcohol in the water. It doesn't have to be in the bath, it can be on a slide, and they float it out that way, and it's a technical trick to get the slide a complete section. Now that will allow me to look at an H & E, but again, because of the issue, it's poorly processed, when we go into antigen retrieval, there's no guarantee that I'll have anything left. We'll end up with those exploding slides or sections.
COFFEY, Q.C.:
Q. And -
DR. MULLEN:
A. And this one, I would probably say it's unacceptable and get something else.
COFFEY, Q.C.:
Q. If we could, and that particular outside case number is 06916-3, I believe. Here, the next page of the exhibit, page four, again the outside case number is S91606 -
DR. MULLEN:
A. Dash 12.

Page 36

COFFEY, Q.C.:
Q. Dash 12. It's April 24th '06, which is about 18 days later, and there's a note here, "the tissue is not well processed."
DR. MULLEN:
A. So this would be after I've said "can't diagnose. Please send another block." They would have sent another block and this would be our comment on the block, and here it's not well processed, a different technology, and unless I actually see the report, I'm not sure whether I would have gone forward or not.
COFFEY, Q.C.:
Q. And just going to go ahead and these are just--these are not at all--what is here, Commissioner, is not at all exhaustive. These are just kind of representative samples of a client satisfaction record, I understand. Page six, Doctor, this particular matter under the comment is "scant tissue in block. Did not trim." What does that refer to?
DR. MULLEN:
A. Sorry, when we receive a block, it's placed in a microtome to basically a razor--equivalent to a razor blade is used or a very sharp

Page 37

instrument is used to take a section at about four to five microns to make the section, and here, the technologist assesses visually the amount of material in the block. If there's only a few cells or a few, a little bit of tissue, they will not try to get a perfect section. They'll make the cut and get whatever they can, because if they trim to make a complete section, they may throw away all that tissue. Trimming is done at a much thicker cut than the final section. It could be done at 10 microns, 20 microns, but the final block or the final section should be about four microns. So they'll try at four microns to get a section. It's to preserve the--or maximize the amount of tissue available for analysis. If this--this may be the only tissue that is available and here, if you look at the outside case number, there is no other block, this was probably a biopsy of some sort. That's the only tissue available. We can't ask for another block. We maximize what we can on this.

COFFEY, Q.C.:

Q. Next page, Commissioner, page seven of the

Page 38

exhibit. This is another client satisfaction record and the reproduction here, make an effort at reading what appears to be there. "The tissue is not well processed. The section explodes upon contact with -

DR. MULLEN:

A. Water.

COFFEY, Q.C.:

Q. Water?

DR. MULLEN:

A. Water, yes.

COFFEY, Q.C.:

Q. So again, this would be the technologist informing you -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. - of the problem with this?

DR. MULLEN:

A. This would be to tell me that I'm going to get an exploding section with the ER and PR.

COFFEY, Q.C.:

Q. Page eight of the exhibit, and again, this is another outside case number. You might be able to -

Page 39

DR. MULLEN:

A. Okay. The block is re-embedded. The block something is--something missing on the--it's -

COFFEY, Q.C.:

Q. It's very difficult to read what's there.

DR. MULLEN:

A. Yes. Can I see the original? Is that any better than the pdf?

COFFEY, Q.C.:

Q. I will check on that.

DR. MULLEN:

A. Oh, so you just have the reproduction. Okay.

COFFEY, Q.C.:

Q. See if it's available.

DR. MULLEN:

A. The block is re-embedded. The block, something not possible remaining and the block is--I really can't.

COFFEY, Q.C.:

Q. So again -

DR. MULLEN:

A. Something is something in the middle.

MR. BROWNE:

Q. Block came out while trimming.

COFFEY, Q.C.:

Page 40

Q. Yes.

DR. MULLEN:

A. Oh, good.

COFFEY, Q.C.:

Q. Good.

DR. MULLEN:

A. Oh, the block--oh so, trimming and the block is something in the--missing? No.

COFFEY, Q.C.:

Q. Something in the middle.

DR. MULLEN:

A. Something is in the middle. So basically, the preparation of the block was so poor that -

COFFEY, Q.C.:

Q. Would that be hollow in the middle, the word "hollow"?

DR. MULLEN:

A. Could be. Could have popped out, because of poor processing. I wouldn't want to -

COFFEY, Q.C.:

Q. Without seeing the original it would be difficult to say?

DR. MULLEN:

A. The original, yes.

COFFEY, Q.C.:

Page 41

Q. And I appreciate that. Again, I'm just going through these for the Commissioner to get some sense of what sorts of communications would go to yourself as the pathologist from the technologist in respect to--I take it these--do these relate to Newfoundland, these--or would you be able to tell?

DR. MULLEN:

A. Did Trish selected them as Newfoundland cases? If she selected them as Newfoundland, they're Newfoundland, yes.

COFFEY, Q.C.:

Q. And page nine, I'm just going to go to. This is--here, the comment is what?

DR. MULLEN:

A. "Tissue is not well processed, leaving it very difficult to cut. Tried to obtain as much tumor on the slides as possible." That again is the--would be the poorly processed. We'd have holes in the H & E sections and possibly the exploding in the--on the ER and PR slides.

COFFEY, Q.C.:

Q. So I'm going--there are others there. If others want to ask you about them, the other lawyers can. I'm just--that's enough for my

Page 42

purposes here, Commissioner. So this sort of form, Doctor, has been used in your laboratory for how long?

DR. MULLEN:

A. As long as I can remember, but let me see at the bottom if it was--this particular form was in 2005. This was updated in 2005.

COFFEY, Q.C.:

Q. It says version four.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. So I take it that there are earlier versions?

DR. MULLEN:

A. Yes. So this is my document. This is our document management immunohistochemistry manual 2005, standard operating procedure 11, document control.doc and version four. So for our accreditation, we have to document all of our operating procedures and all of our forms and then we also have to document this type of quality assurance or quality control program.

COFFEY, Q.C.:

Q. So this sort of form has been used in one form or another -

Page 43

DR. MULLEN:

A. Oh yes.

COFFEY, Q.C.:

Q. - for a while, quite a while?

DR. MULLEN:

A. Yes. As I mentioned, it's used both in the routine histology, as well as in the special areas, special histology areas.

COFFEY, Q.C.:

Q. If we could, please, Registrar, take you now, Doctor, to Exhibit 18--P-1840. Now Doctor, this is a letter you wrote April 14th, 2008, up on the screen there yesterday. It's signed by yourself. Could you tell the Commissioner, please, how you came--and I'm going to refer to this as a slide review.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Shorthand. How you came to do this slide review?

DR. MULLEN:

A. When co-counsel were in Toronto, they indicated in December to review the results of my findings on the retrospective study. In

Page 44

other words, the blocks, the 1106 blocks--11--yeah, 1106 blocks that were referred to Toronto for restaining and interpretation. They indicated they had an interest in reviewing--have someone review the original material. So those, when I talk about the--speak about the original material, I'm referring to the H & E sections and the ER/PR and external controls of the material that was stained in St. John's over that time period, from '07 to--sorry, '97 to '05, if I remember correctly. At that time, they indicated they were thinking of like 3,000 slides, so all of the original material.

COFFEY, Q.C.:

Q. And you were then subsequently asked to do what?

DR. MULLEN:

A. To review a selection of these slides, which turned out to be 550--approximately 540, well, 547, something, somewhere around there. 500 some odd slides, which were the--oh, sorry, 539 cases and I think there were 547 slides. I was asked to review the H & E, the ER, PR, external controls when available, and the

Page 45

pathology report when available, and to comment on the--basically, to repeat my--the process of diagnosis of the tumor, the percentage ER positive, the percentage PR positive, presence/absence of internal controls, whether they stained, if they were present, or stained weakly, the presence--my assessment of the adequacy, and then to comment on the external controls, when available, whether they stained or didn't stain. Then to look at the pathology report and if I could glean from the original pathology report, a numeric value or a qualitative value for ER/PR, to enter that, and then I looked at the pathology report that I was presented with. If it had some reference to my reinterpretation and a proportion had a reference to my reinterpretation of the material, it would say something to the effect that the slides were stained in Mount Sinai hospital and Dr. Mullen reported this and this, I would enter them. I would make a comment whether they were concordant with the original interpretation in Newfoundland and then I would make some--or

Page 46

discordant and I'd make some comment, if they were discordant, whether--about the internal control presence or absence. So it's--once we see the spreadsheet, it'll become more obvious or clearer than what I'm saying now. So 539 cases, basically the same process, extended to commenting where I could on discordance and concordance. I did not go back to my original material, the spreadsheet that I presented, and actually check what I had said. It was only if it was there.

COFFEY, Q.C.:

Q. Now just on that point, and I'll be exploring this a bit more with you as we go ahead, that in determining concordance or discordance as you've referred to it -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. - you were utilizing whatever information was on the pathology report that you had received from Newfoundland in 2008.

DR. MULLEN:

A. That is correct.

COFFEY, Q.C.:

Page 47

Q. And if the pathology report from Newfoundland that you received did refer to Mount Sinai's retrospective results, and they were included there, you would read what was written there and compare it to what you were seeing--what was written there with what you were seeing?

DR. MULLEN:

A. What the--yes.

COFFEY, Q.C.:

Q. In the original report?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Pathology report, back in 1998, '99, 2000 or whatever.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. On the same--because it would be in the same pathology report?

DR. MULLEN:

A. Yes, yes, the original would be--the original values--well, when we see the spreadsheet--I can't--I didn't--don't recall the percentage, but a vast majority of the--I should say, a

Page 48

large number of the cases had just qualitative, whether it was negative, completely negative or mostly negative type comments. I wasn't quite sure what those meant.

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. Because having learnt in December that there were different cut points used for what was considered negative, I really couldn't comment on that.

COFFEY, Q.C.:

Q. So -

DR. MULLEN:

A. And when I talk about cut points, I'm talking about greater than 30 for ER, then greater than 10.

COFFEY, Q.C.:

Q. Now, what I'm going to do, and I'll approach it this way, I'm going to take you through the two-page report.

DR. MULLEN:

A. Okay.

COFFEY, Q.C.:

Page 49

Q. And then go to the spreadsheet of the results you prepared from the slide review and then perhaps, as necessary, return to the report. Just to look at the first page of the April 14th, 2008, Doctor. So you report here that you completed your review of five banker boxes containing in total 24 individual slide boxes and related original pathology reports were available. And you indicate that in mid April that was being returned to the Commission of Inquiry offices. Doctor, you refer to 539 cases. Would that be 539--what do you mean by a case in this context?

DR. MULLEN:

A. Oh, 539 patient specimens.

COFFEY, Q.C.:

Q. So for any one patient specimen, how many slides would there be, generally?

DR. MULLEN:

A. Okay. Anywhere from two, ER/PR, to one, two, three, four, I'd say some had nine, I think up to nine, but the vast majority would have an H&E, an ER and PR, so there would be three. Some would have an external control of either ER and/or PR or both. And some cases I would

Page 50

have two sets of stains for, one H&E, two sets of stains for ER/PR and two sets of stains for the external controls for the ER/PR, so that would be one, four, five, seven, nine, so, yes, nine.

COFFEY, Q.C.:

Q. In some. I take it there weren't many that -

DR. MULLEN:

A. No, there were very few. And when see the spreadsheet it will become obvious. And some I would have the ERs control, external control, some I'd have the PR and some I said both.

COFFEY, Q.C.:

Q. Now, Doctor, here then you indicate that the results of your review are enclosed on a compact disc. And if you could just then take us, you say here that the disc contains an Excel spreadsheet labelled "Mount Sinai review by year."

DR. MULLEN:

A. Um-hm.

COFFEY, Q.C.:

Q. With sheet one labelled "NLCOIHR" and sheet two labelled "MSH data." And "NLCOIHR

Page 51

contains your original data forwarded to me for review," okay, so that's a spreadsheet the Commission had sent you. "MSH data contains the results of my" that would be your review?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. "With additions and corrections as required. The patients are arranged alphabetically by year. The additions are indicated by either an asterisk after the number or the term Zymed or DAKO. The asterisk additions were necessitated by additional slides submitted with a separate block number. Zymed and DAKO additions were required because of the presence of duplicate slides on the same block with different immunohistochemical staining. The corrections involve year and block numbers. I've also enclosed a copy of the MSH data spreadsheet code which explains the terms used in the results section of the MSH data spreadsheet." So now if I could, having taken you through that, I just read it out to you, if we could, please, bring up, please, Exhibit P-1837? Just this is page 1 of the exhibit.

Page 52

The reference to DAKO and Zymed.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. You see that?

DR. MULLEN:

A. Case 1236, it's one, two, three, four, five and six down and then--I should have said Kit, as well, I missed that one.

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. I had slides that were ER/PR labelled and they also had DAKO and Zymed and then DAKO and Kit. I wasn't quite sure what they meant, so I--and these were from '97, so I--to separate the reports, I put, I duplicated the demographics, the name, MCP number, date of birth and the block number, specimen number and block, year number, and then interpret them on different lines. Every time I had a slide, I would give an interpretation. I didn't average them, I didn't take the higher, didn't take the lower, whatever I had, there's a number.

COFFEY, Q.C.:

Page 53

Q. Okay. Now, just go back then, please, to Exhibit P-1840? Now here, Doctor, beginning at the bottom of the first page you say "To summarize my observations, the overwhelming majority of cases had one or more of the following problems: Poor fixation or processing resulting in incomplete tissue sections; loss of the internal structure of the nucleus and staining restricted to the periphery of the slide. In our previous conversation I take that's you're referring to the interview that -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. That occurred involving yourself and Ms. Chaytor and I in December of '07. The incomplete tissue section issue was referred to as, in quote, "exploding", sections. The exploding term is your term, I take it?

DR. MULLEN:

A. Yes, yes. There is a proper term, but the-- you don't use that in literature, but.

COFFEY, Q.C.:

Q. You wouldn't have used the word "exploding".

Page 54

What would that be referred to as, Doctor, in the proper term, do you know?

DR. MULLEN:

A. Poor adherence.

COFFEY, Q.C.:

Q. Poor adherence.

DR. MULLEN:

A. Poor adherence.

COFFEY, Q.C.:

Q. That would be sections with poor adherence?

DR. MULLEN:

A. Yes, a section would not stain the slide. I like the exploding, it's more graphic.

COFFEY, Q.C.:

Q. In some of the material I reviewed, the exploding sections resulted in a loss of the invasion tumor on the ER/PR slides although it was present in the initial H&E section. I take it you referred to that -

DR. MULLEN:

A. Yes, if you recall when I was going through the pathology 101, because of antigen retrieval for ER and PR, it requires heating in an acid solution, the material doesn't adhere to the slide. It falls off. So,

Page 55

although you can get a section, an adequate or semi-adequate or section for a--the routine H&E, once you require any pre-treatment or before you stain any of the antigen retrieval processes, your chance of losing the section is quite high. And it results in that portions of the slide falling off, portions of the slide adhering to each other, rendering interpretation either not--you're unable to interpret or it's very difficult to interpret.

COFFEY, Q.C.:

Q. You go on to say here then that the second issue, "loss of the internal structure of the nucleus, we discussed as 'hollow' nuclei" and I take it that's it the same context, the "we" is, the -

DR. MULLEN:

A. Yes, you and Ms. Chaytor and Mr. Simmons.

COFFEY, Q.C.:

Q. Yes, Mr. Simmons was there for Eastern Health as well during the interview.

DR. MULLEN:

A. And my lawyer, Mr. Clements.

COFFEY, Q.C.:

Page 56

Q. Yes.

DR. MULLEN:

A. I have to acknowledge my lawyer.

COFFEY, Q.C.:

Q. Mr. Clements was certainly also present. We discussed as "hollow" and I believe the word "hollow" was your term?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. And what is that?

DR. MULLEN:

A. That's the hollow nuclei. That's the leaching out or the loss of the nuclear structure, the contents of the nucleoplasm which is chromatin, the DNA and all the proteins within the nucleus. So -

COFFEY, Q.C.:

Q. And that is caused by, generally -

DR. MULLEN:

A. Poor fixation processing. It's what we call autolysis, the tissue is actually digesting itself.

COFFEY, Q.C.:

Q. You continue by saying, "because of poor

Page 57

fixation, the nuclear substance is lost and markedly deceases the chance of staining for ER/PR". And I take it here, poor fixation includes potentially processing as well.

DR. MULLEN:

A. Yes, sorry, yes.

COFFEY, Q.C.:

Q. The third issue -

DR. MULLEN:

A. No, sorry, that would be a fixation only, for the hollow nuclei because if you have it, if it's fixed, it's there. The processing, you wouldn't get that part of the section. Sorry, to clarify, yes, this one I could tell would be fixation.

COFFEY, Q.C.:

Q. Where you're seeing a situation involving hollow nuclei.

DR. MULLEN:

A. Hollow nuclei, yes.

COFFEY, Q.C.:

Q. It's a fixation issue or problem.

DR. MULLEN:

A. Yes. It would be aggravated by poor processing, but it's mainly a fixation.

Page 58

COFFEY, Q.C.:

Q. You go on to say then, "the third issue, staining restricted to the periphery of the slide refers to staining of the periphery of the section with absence of staining centrally".

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. And you continue by saying, "it is difficult to interpret the results of these cases as the peripheral staining results may not reflect the results of the entire tumor". What does that -

DR. MULLEN:

A. Again, if you go back to my peach analogy and the third section where I had the complete section of the tumor. Depending on how the specimen was grossed, in other words, how it was cut or if it wasn't cut or how thick the sections were or whether it was sectioned at all, it reflects the fact that the formalin has fixed the outside, but not the inside of the tumor. So, if I took a section through the middle of my--can I pull up the

Page 59

PowerPoint, sorry, I apologize. It's just easier to show it graphically. Okay. So, if this is sectioned, I would take a section through or the pathologist assistant would select this block--now when I say this block, this is what would be put through the processor to make a block. Now -

COFFEY, Q.C.:

Q. That little portion of this you just outlined -

DR. MULLEN:

A. Yes, that would be the tumor and some adjacent normal tissue. In this case, it's mostly fat. If this were, I mean, you have to use your imagination, if this were the closest distance or any--the fixative, if this were the complete peach, the closest distance is to here. So, depending on the time of fixation, I might end up with basically a rim of fixation here and nothing in the centre.

COFFEY, Q.C.:

Q. No proper fixation.

DR. MULLEN:

A. No proper fixation. So, we would end up with this type of this centrally and a little bit

Page 60

of viable tumor at the periphery. So, this part would be necrotic and the outside would be fixed properly. And if you recall yesterday, there was the exchange of e-mails. In one case I explained that in one section I really only had staining at the periphery and the other section where I changed the value, it was a little higher, I also had some identifiable, better preserved tumor.

So, if you think of a sphere, if you're coming in from the outside, the margin--if I only take a section of the margin, cut off the tip of it, that will, theoretically, be uniformly fixed, but as I move towards the centre as the formalin moves in, I will have unfixed tissue centrally. And I need fixed tissue, well processed tissue for the stain.

COFFEY, Q.C.:

Q. And would you go back, please, Exhibit P-1840, thank you.

DR. MULLEN:

A. And the last line, "it's difficult to interpret results and peripheral staining may not reflect". And that was in the back and forth e-mails with, I believe it was Doctor

Page 61

Cook. And that would be, I take it, that exchange of e-mails would be representative of the sort of phenomenon you're talking about here?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. In terms of the overall retrospective study, would it be limited to that one case or would -

DR. MULLEN:

A. Oh, no, no, no. This whole series were present in upwards of 90 percent. I mean, it was across the board. I mean, not each case had all three, the poor fixation processing with the explosion or the hollow or the doughnut issue for the peripheral staining, but the majority had the fixation processing with the hollow. A large proportion had the exploding and small proportion had the doughnut or absence the central staining.

COFFEY, Q.C.:

Q. And if we could then, Doctor, you go on then to, in paragraph 2, you say--and this is in the slide review, you're looking at now.

Page 62

DR. MULLEN:

A. Yes, of the original stained slides.

COFFEY, Q.C.:

Q. Yes, the original stained slides, originally stained in Newfoundland, at least, you understood.

DR. MULLEN:

A. Yes, um-hm.

COFFEY, Q.C.:

Q. You write here, paragraph two, page two of the exhibit, "absence of the internal controls, many of the cases had no normally duct epithelium to use as an internal control on the initial H&E section. Additionally, in many cases where the original H&E section had normal duct epithelium, it was not present on the ER/PR slides as a result of the exploding section issue".

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. So, would you expand upon that a little bit for the Commissioner.

DR. MULLEN:

A. Okay. Registrar, can I have the PowerPoint

Page 63

popped up again, please. So, if this is the type of section that I'd see on an H&E, I would be able to identify tumor. I would be able to identify the normal duct epithelium, if it were present. Then when I went to match that to this, this is--I apologize, this is not the concordance slide with--this is not the ER that goes with that H&E, but if I were trying to match, I would be looking here for the invasive tumor. I'd be looking here for the normal duct epithelium and there would be large areas of the section that were missing. So, normal duct epithelium isn't that prevalent. I would lose it. And here it would be virtually impossible to find any. You might have a few residual, either tumor or duct epithelium up here, but the vast majority of this, there's nothing there to interpret.

COFFEY, Q.C.:

Q. So, if we can go back then, please, to Exhibit P-1840. Thank you. So, here under the "absence of the external controls", many of the cases you note had no normal duct epithelium to use as an internal control on the initial H&E section. I take it then that

Page 64

that particular block which was used to grade the H&E section that you were looking at, the slide that had been prepared two or perhaps five years or whatever before in Newfoundland. Looking at the H&E section slide, there just wasn't any, that you could see, normal duct epithelium there.

DR. MULLEN:

A. Um-hm.

COFFEY, Q.C.:

Q. And then in cases where there was, on the H&E slide, at times when you looked at the matching ER and PR slides, ER and PR slide did not have the tissue that had originally on the H&E slide had contained normal duct epithelium was missing -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. - on the ER and PR slides.

DR. MULLEN:

A. A portion you can explain by--we talk about our white swan, the section that--you're getting another section. It may not be in that. And in rare cases where I didn't find

Page 65

normal duct epithelium in the H&E section, I might have found it in the ER or PR. So, I assess the three slides for the presence of normal duct epithelium.

COFFEY, Q.C.:

Q. Okay. Overall, many of the cases just--as you note, either had none on the H&E section that you could see or by the time it made it to the ER/PR slides, you couldn't see any normal duct epithelium on the original slides.

DR. MULLEN:

A. That is correct.

COFFEY, Q.C.:

Q. Paragraph three is, written here, "negative internal controls, in many cases, the internal control either did not stain or stain very weakly. Also with the exception of a small minority of cases, the ER internal control was significantly weaker than the PR internal control". Now, I take it again, to remind the Commissioner and those present here that you're looking at the original Newfoundland slides?

DR. MULLEN:

A. Yes, that is correct.

Page 66

COFFEY, Q.C.:

Q. In saying this.

DR. MULLEN:

A. Yes. And the PowerPoint or not, is it worth it, Commissioner?

THE COMMISSIONER:

Q. Yes.

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. Okay, back we go. So, again, I would look, the H&E, looking for an internal control which we have here, the Sinai case, the tumor here, I think that's malignant epithelium. I don't think I have benign internal control in this section. That wasn't what I was doing. Again, malignant. Here malignant staining, looking at the internal control and here, I am happy with the case from Newfoundland that there was benign epithelium and it did stain. So, this is what I'm referring to, looking at that benign epithelium, that it did stain and then I would assess the tumor. But unfortunately, I don't have a side-by-side comparison of ER and PR, but uniformly PR was

Page 67

stronger than ER. The ER stain was quite weak.

COFFEY, Q.C.:

Q. And that's in the internal controls.

DR. MULLEN:

A. Yes, internal and in the external controls.

COFFEY, Q.C.:

Q. Okay. What, if any significance in looking at that, did that have? Did that mean anything to you at the time?

DR. MULLEN:

A. Well, I would be worried that the stains hadn't been optimized and the validation hadn't been carried out properly, that I would be--the staining might not reflect the biology, to put it in as broad a context as possible, that if the ER stain hadn't been optimized and validated properly, we weren't staining appropriately.

COFFEY, Q.C.:

Q. "We" in the sense -

DR. MULLEN:

A. "We" meaning Newfoundland.

COFFEY, Q.C.:

Q. Back, historically.

Page 68

DR. MULLEN:

A. Yeah, the historical.

COFFEY, Q.C.:

Q. And Doctor, under optimized conditions generally what you would expect to find in terms of staining of internal controls for ER and staining of internal controls for PR in terms of their intensity levels?

DR. MULLEN:

A. I would expect them to be--if I'd optimized them approximately equal, you might accept slight variabilities; one being stronger, one being slighter weaker. But you would want to optimize to the same level or as close to the level as possible.

COFFEY, Q.C.:

Q. And here in the slide review that you were conducting, you did make a point of noting that -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. - or looking at multiplicity of slides, well over 500 ER slides and well over 500 PR slides, that--where there were internal

Page 69

controls and where the internal controls did stain, you noted that the ER internal control tended to be significantly weaker than the PR.

DR. MULLEN:

A. That's correct.

COFFEY, Q.C.:

Q. Doctor, looking at, and the fact that there were some, apparently, based on your observations, you refer, many of the cases had no--paragraph two, if I could, P-1840, thank you. "Many of the cases had no normal duct epithelium to use as an internal control on the initial H&E section".

DR. MULLEN:

A. Um-Hm.

COFFEY, Q.C.:

Q. Doctor, were you surprised by that? Was that expected?

DR. MULLEN:

A. No, no. The breast as well as for, I mean, the object in immunohistochemistry is to have controls. External controls are fine, they're mandatory, but the internal control really reflects the tissue from the time it has been removed from the patient to the time the slide

Page 70

arrives on your desk. They go hand in hand or they're through the same slide, same processing. Now, what do we use internals controls--skin, if I'm looking at--there are certain things that have built in internal controls If I'm doing controls for nerves, if I'm looking at a tumor and trying to see if there are nerves in it, it has neural differentiation, there may be benign nerves. If I'm looking at a keratin which marks for basically skin or derivatives of skin, if I have an internal control that has skin in it, that sort thing, you try to maximize your section by having both a built in internal control as well as the tumor. In many cases you can't have that control, but in breast, a large proportion of cases, especially in the pre-menopausal or the early post menopausal phase, it's only when we get quite, after the post menopausal phase, when there's lots of atrophy of the normal duct epithelium or loss of the normal duct epithelium, that you may not have the internal control. But you try to maximize, you try to select your slide to have the internal control. As they go along, the

Page 71

benign and the malignant are processed, are handled, fixed, processed, stained the same way and then the interpretation. It helps me establish my confidence in the interpretation.

COFFEY, Q.C.:

Q. Doctor, looking at paragraph three, were or was on the original slides, on the original ER slides and original PR slides that you looked at in the slide review, were there was internal control tissue, normal duct epithelium there, present, and you noted, looking at the original slides that it did not stain, the internal control tissue did not stain. As a pathologist doing an ER examination and a PR examination and seeing the internal control tissue present, but not staining, what, if anything, in your view, would that cause or should that cause a pathologist to do?

DR. MULLEN:

A. Again, it's not an absolute.

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. But as I mentioned, post menopausal,

Page 72

approximately 90 percent, 88.8 or 9 percent, basically 90 and the pre-menopausal about 80 percent have at least one percent of the epithelium stain. Again, one case acceptable, but I would have to look at sort of, a sequence. If they're always turning up negative, then I'd be very worried. Now, a sequence could be as short as three or as long as ten, that type of thing, but it's something I would keep in mind, my internals controls aren't working. I would comment on the--if you remember the synoptic reports we have, there is a comment that basically the--I mean, it's so obvious, not obvious, it's so consistent that our default is normal breast tissue was present to assess the internal or normal breast tissue reacted with the ER and PR stains. It's very rare that I actually go in and say, normal breast, except for metastatic carcinoma, I say, normal breast tissues are present. It's very rare that I say normal duct epithelium is not present and then it's even rarer that the breast tissue did not react with. So, it's an outlier or it's an infrequent finding and therefore,

Page 73

would alert me to be very careful.
COFFEY, Q.C.:
Q. And in a situation where you are seeing what you interpreted as fixation and/or processing artifacts -
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. - combined with an internal control that hadn't stained, what if anything -
DR. MULLEN:
A. You're asking for trouble. You really are asking for trouble trying to interpret that type of tissue. I mean, that would--going back to my one, two, three from yesterday, that would trigger, "whop", back we go; what are we doing wrong? What is going wrong?
COFFEY, Q.C.:
Q. Paragraph four, you've written, "stained deposit obscuring morphology. In many cases, excess stain was present either on the surface or beneath this section, both artifacts preclude assessment of the ER/PR staining in the areas affected". First of all, tell the Commissioner, what morphology is, first of

Page 74

all.
DR. MULLEN:
A. Morphology refers to the histology, the actual substance of the slide. If you recall, my PowerPoint again, okay, so when I talk about morphology, I'm talking about the histology. I can see ducts here. I can see cancer here. I can see normal here. If I threw brown stain on top that non-specifically adhered to the surface or somehow or other was--because the slide wasn't even, was underneath the section, I would have--basically, if I threw paint on the floor, you can't see the texture of the carpet. That's the issue that you have, brown on top of brown and you're not sure, is it restricted to the nucleus or is it a non-specific. So, that whole area you have to throw out from an interpretation and that can either because a slide was uneven and stain is present underneath or it wasn't properly washed from the slide. And that's another--that wasn't that common, but it did occur. And it's -
COFFEY, Q.C.:
Q. And I take it that it makes those particular

Page 75

portions of the slide, where that occurs unreadable.
DR. MULLEN:
A. Uninterpretable.
COFFEY, Q.C.:
Q. Uninterpretable.
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. Paragraph 5 in P-1840, page two reads, "external controls, the externals controls were inconsistent both between slides and within slides. In some cases the positive cells were barely stained. In occasional cases from 2005, the control stained both the nucleus and the cytoplasm, reflecting inadequate or incorrect validation." Could you elaborate upon that for the Commissioner, please?
DR. MULLEN:
A. Yes, the external controls are run, I'm not sure of the protocols, but the external controls are run with each batch of slides. And I believe in all of the cases from St. John's, it was a tumor that was used as an

Page 76

external control, it was a tumor that was positive for ER and PR. There were various--I don't know if it was the same tumor or various tumors, but it was the control, and interestingly it wasn't an uniformed staining, either with the ER or the PR and the intensity and the positivity rate or positivity--the number of cells that were positive varied, it wasn't uniform across the slide, it varied from area to area and in some cases, not that many, very few of the tumor cells were positive. In one or two, I believe, I was questioned whether they were even positive, whether the external control was positive. So it would not be the type of external control I would like. We use benign, we use endometrium or endocervix that the nuclei and the--well the endometrium, rather, the nuclei are positive in the endometrial cells, as well as the smooth muscle cells are positive and those are the type of control. It's not dependent on a tumor, so that was variability, some--questionable whether they're actually positive.
COFFEY, Q.C.:

Page 77

Q. Okay.
DR. MULLEN:
A. And in occasional cases from 2005 -
COFFEY, Q.C.:
Q. If I could, Doctor, before you go on to that last sentence, so the second sentence here, the external controls were inconsistent both between slides and within slides.
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. That is between the control slides?
DR. MULLEN:
A. Yes, so if I had--when we see the spreadsheet again, if I have a control slide with case one from '97 and I had a control slide from case five of '97, they were not equivalent.
COFFEY, Q.C.:
Q. The external controls.
DR. MULLEN:
A. The external controls were not equivalent, the staining was not equivalent and then within case one, the stain from area to area was not equivalent -
COFFEY, Q.C.:

Page 78

Q. Within the external control slides.
DR. MULLEN:
A. Within the external control slides. In some areas it was total absence of it; in other areas it would be strong; in other areas it would be questionable. And so both between and within the individual slides, there was variability.
COFFEY, Q.C.:
Q. And that's the individual control slides in this context?
DR. MULLEN:
A. Yes, that's correct.
COFFEY, Q.C.:
Q. I'm sorry, Doctor, the last sentence, paragraph five?
DR. MULLEN:
A. The occasional case from 2005, now I didn't have an indication that they had changed--"they" meaning St. John's, had changed their processing, but these slides were labelled with bar codes, so I, from experience from other hospitals, we use the DAKO, as I mentioned earlier, I thought these were probably the Ventana stains and both the

Page 79

major--well, there weren't that many cases, but some of the cases, both the nucleus and the cytoplasm stained, so that would have reflected either inadequate or incorrect validation. When we validate--or when we optimize and validate our immunohistochemistry stains, we want to have sensitivity and specificity. Here we had staining of both the nucleus which is appropriate, but staining of the cytoplasm, which is inappropriate.
COFFEY, Q.C.:
Q. And this is in respect of the controls?
DR. MULLEN:
A. Yes, the controls. So if you don't have an adequately stained control, then you cannot interpret the material.
COFFEY, Q.C.:
Q. This variability in the staining of the external controls as between the external controls or even within a particular external control slide, what, if anything, as a pathologist, you know, if you came across that, you know, in your own daily work, what, if anything, would that cause you to do? If you saw the equivalent slide, for example, at

Page 80

Mount Sinai?
DR. MULLEN:
A. The Sinai, I don't know if Ms. Wegrynowski mentioned that the technologists evaluate the external controls, so we would not see the external controls unless we had some reason to ask to see them. It's the responsibility of the technologist to review the external controls, to be satisfied that they meet the standards that have been established in conjunction with the pathologist. So the technologist and pathologist have established guidelines and if they don't meet them, they won't give me the slide. I would not have seen this case until the external control had stained appropriately and they were satisfied.
Now that's doesn't preclude me from looking at the slide when I received it, asking to--not being satisfied, asking to see the external control and sending it back to have repeated. But the first gatekeeper and the most important gatekeeper is the technologist who reviews the controls, both internal and external.
COFFEY, Q.C.:

Page 81

Q. And the external controls -
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. - if one such external control slide, you did for some reason go and ask to see an external control slide and it was brought to you and you saw this sort of variability in staining of an external control slide which you did witness in some of the Newfoundland slides, what, if anything, would that cause you to do?
DR. MULLEN:
A. Just to go back to the Sinai, the external controls are benign tissue, the endometrium. So I know that everything should be staining. It should be uniform across the slide. If I have a section, the epithelia cells, the muscle cells should stain. If I have large areas of the slide which I saw equivalent in Newfoundland, I would be worried that the machine wasn't dispensing correctly, that only areas of the slide were being covered or some--there was some biological or not biological, some--it would be a technical issue with the dispensing of the machine or the preparation

Page 82

of the slide that was causing the stain. But because they were using tumor slides, I--it's difficult to interpret properly. So the selection of the external control is very important. It has to allow you to assess the staining, both the reactivity as well as the extent of the staining.
COFFEY, Q.C.:
Q. Paragraph six, you say there was a--you go on to say here, "discrepancy between internal and external controls in only one or two of the 539 cases I reviewed was the staining in the internal control as strong as the corresponding external control." And what are you referring to there, Doctor?
DR. MULLEN:
A. That if you recall, the internal controls were never as strong as the external controls. I would like to see my internal controls, if you recall from my cases, the internal and the tumor were the same.
COFFEY, Q.C.:
Q. Yes, that is the Mount Sinai slide you showed us?
DR. MULLEN:

Page 83

A. Yes, yes. So if--let's separate these two. This we'll say will have--rather than having one slide, I'll divide it here as two slides. This would be the equivalent of an external control. I would like to see my external control, the staining and the internal control of the internal--sorry, the internal control of (unintelligible) epithelium be equivalent intensity, just to show that the processing and reactivity were the same. It doesn't necessarily have to be exact, but it should be in the same ballpark. But I was getting at the--from Newfoundland, using this slide as an example, that this, the external control--the internal control, if we use the tumor here, would be less than the external control. So it was always significantly less, questioning whether the processing fixation handling were equivalent.
COFFEY, Q.C.:
Q. Of the -
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. - the external control tissue and then -

Page 84

DR. MULLEN:
A. And the internal control. I know that the internal and the tumor are handled essentially the same because they're on the same slide, but the external control, the slide was not stained at the same time because it wasn't--they weren't--the internal control, or sorry, the external control was not on the same slide so it wasn't stained the same time and the processing obviously, the fixation and processing were different because the tumor would have been removed before and a block, sort of a control block was kept and would be sliced as needed.
COFFEY, Q.C.:
Q. Now Doctor, you go on--if we go back, please, to 1840, page two, thank you. You go on to conclude by saying "there were very few cases in which there was a significant difference in my observation compared to that recorded on the original report. Some of my observations were higher than those recorded and some lower." Now again, I'll be referring to the report to put this paragraph in context, but you indicate that "there were very few cases,"

Page 85

that would be of the 539?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. "in which there was a significant difference in my observation," that would be your observation of what?
DR. MULLEN:
A. Of the original H & E, ER and PR stained slides from Newfoundland.
COFFEY, Q.C.:
Q. Okay, what are you're looking at through the scope?
DR. MULLEN:
A. Yes, and -
COFFEY, Q.C.:
Q. Your interpretation, very few cases in which there was any significant difference in your observation of what you saw and observed of the Newfoundland, original Newfoundland slides, compared to what was recorded on the original report?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:

Page 86

Q. And this refers to, I take it, percentages and things like that?
DR. MULLEN:
A. Yes. I was a--I had great difficulty--I certainly couldn't do statistics because I'd learnt my lesson from preparing the statistics from your first visit, but I didn't know what--Newfoundland was more qualitative rather than quantitative. When we see the spreadsheet--I can't--off the top of my head, I can't remember the exact percentages, but they use terms "negative" and I didn't know what a negative meant. Was it 30, 10 or less than one? So that was--so I sort of tried to guestimate whether it was that sort of thing, but when I say significant difference, I'm saying that I said it was zero and they said it was like 100, that type of thing, or zero. It would be one category greater zero, and they'd say 20 or 30 or 40, or I would say 20 and they'd say zero. So that, it--you would need a statistician. You would need what the original cut offs were to qualify that statement. But it's just sort of ballpark. The interpretation didn't appear to be an

Page 87

issue.
COFFEY, Q.C.:
Q. Interpretation in the sense of -
DR. MULLEN:
A. Of the pathologists -
COFFEY, Q.C.:
Q. - arriving at a percentage?
DR. MULLEN:
A. Yes, the pathologist interpreting that slide and coming up with a number. We seemed to be fairly good correlation.
COFFEY, Q.C.:
Q. Now whether or not the slide should have been interpreted at all, I take it -
DR. MULLEN:
A. That's a different matter.
COFFEY, Q.C.:
Q. - that's a different issue?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. Okay, and I say, that's the original slides.
DR. MULLEN:
A. Yes, these are the original slides.
COFFEY, Q.C.:

Page 88

Q. Commissioner, I'm going to ask now if we could go, please, bring up page three of this exhibit please? Thank you. This, I take it, is the MSH data spreadsheet code?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. And Doctor, I'm going to be asking you, Registrar, to switch back and forth then between this and Exhibit P-1837. Now, here, Doctor -
THE COMMISSIONER:
Q. Mr. Coffey, it's about 11, so I'll leave it to you to decide whether you want to launch into this exhibit before the break and interrupt or -
COFFEY, Q.C.:
Q. If I could -
THE COMMISSIONER:
Q. - whether you would prefer to -
COFFEY, Q.C.:
Q. - one heading and then we'll have a break, Commissioner.
THE COMMISSIONER:
Q. Okay.

Page 89

COFFEY, Q.C.:
Q. And the heading of this is "Dr. Brendan Mullen, review of the five banker boxes containing 24 individual slide boxes and related original pathology reports, where available."
DR. MULLEN:
A. Yeah.
COFFEY, Q.C.:
Q. "From Eastern Health. Received by the Commission of Inquiry on hormone receptor testing on April -
DR. MULLEN:
A. April 14th.
COFFEY, Q.C.:
Q. - April 14th, I'm sorry, 2008. So this is-- these spreadsheets. This is a spreadsheet. If we could--there's a bunch of--and at page 16 of the exhibit, then it goes on through page 30, there is--beginning at page 16, there's a heading "Newfoundland and Labrador pathology review of original slides provided by Eastern Health to Dr. Brendan Mullen, Mount Sinai Hospital." So I take it there was a spreadsheet that accompanied the material, the

Page 90

slides, and what pathology reports were sent to you?
DR. MULLEN:
A. Yes, that is correct.
COFFEY, Q.C.:
Q. Original pathology reports were sent to you, and you prepared then your own spreadsheet?
DR. MULLEN:
A. Yeah, to facilitate reporting, I--the cases by and large were divided by years, but to facilitate reporting, they were not in any order. I put them alphabetically, so I would see the name. This has all been redacted. I'd see the name and then--so it was just easier for me to enter the data. This was a labour of--should be something called love, but it was a lot of work.
COFFEY, Q.C.:
Q. Commissioner, if we could break then?
THE COMMISSIONER:
Q. All right then, we'll take the morning break.
(RECESS)
THE COMMISSIONER:
Q. Please be seated. Mr. Coffey.
COFFEY, Q.C.:

Page 91

Q. Thank you, Commissioner. Now Doctor, here on this spreadsheet, at page one of Exhibit P-1837, there is--I'm going to go across the headings at the top of the first page. There's an ID number. Do you know what that ID number is?
DR. MULLEN:
A. This was provided to me on the original spreadsheet.
COFFEY, Q.C.:
Q. Okay, and that's the one coming out of Newfoundland?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. The copy, the original slides.
DR. MULLEN:
A. NL, sorry.
COFFEY, Q.C.:
Q. Sure.
DR. MULLEN:
A. I had seen the copy of my letter, it was -
COFFEY, Q.C.:
Q. 1840, page one, Registrar, please? There you are.

Page 92

DR. MULLEN:
A. Yes, sorry. It was provided to me on NLCI Newfoundland Commission of Inquiry Hormone Receptor.
COFFEY, Q.C.:
Q. Okay, and if we could go back then, Registrar, please, to Exhibit 1837? Then of course, the name, I take it, would be the patient's name -
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. - as reported to you. The MCP number and the date of birth is reported to you?
DR. MULLEN:
A. Yes, provided to me, yes.
COFFEY, Q.C.:
Q. Provided to you. And then the specimen number is listed here in a column. I take it this would be a specimen number which was provided to you?
DR. MULLEN:
A. Yes, it would be either on the--it would be on the pathology report, if the pathology report was forwarded, and it would be on the block that I received--sorry, not on the block,

Page 93

sorry, referring now to the slide, the slides that I received. So it would have the specimen number and it would also, in some cases, have the block number dash A, and the N/A if there was not--if there was no identifying block number.

COFFEY, Q.C.:

Q. No identifying block number on the slide itself?

DR. MULLEN:

A. Yes, that's correct.

COFFEY, Q.C.:

Q. Okay, so here then, the year specimen is--these are the '97 which would correspond, I take it, to the '97 as part of the specimen number?

DR. MULLEN:

A. Yes, that's correct.

COFFEY, Q.C.:

Q. The referral number, what is that, do you know?

DR. MULLEN:

A. That would be an internal number from St. John's. I don't know what that refers to.

COFFEY, Q.C.:

Page 94

Q. And this is just--again, this was on the spreadsheet that accompanied the slides on their way to you?

DR. MULLEN:

A. Yes, that's correct.

COFFEY, Q.C.:

Q. Then the blocks, a heading blocks, which is, I take it, the block number associated with the particular specimen number and the slide?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Okay, then this heading here, if I could--sorry, about that.

DR. MULLEN:

A. No, that's fine.

COFFEY, Q.C.:

Q. So we go across the page here, there's MSH review, and then there's a heading HE, ER, PR, IC, F/P and EC. Could you take us through each of those?

DR. MULLEN:

A. The MSH review refers to my, Mount Sinai Hospital review, which is basically Mullen's review. The HE should actually be H & E.

Page 95

That was the original stained slide, and I would make a--and then the D, DTD, etcetera, refers to the code that was provided. It's basically the same as the code that we used for the retrospective review. I mean, there were one or two additions and one or two subtractions because we didn't have the same spread of tumors.

COFFEY, Q.C.:

Q. If I could, please, while we're on this, so this HE is referring, in effect, and in fact, to H & E?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. And what is entered here, under the overall column heading of MSH review, which as you point out is really Dr. Mullen review -

DR. MULLEN:

A. Um-hm.

COFFEY, Q.C.:

Q. - particularized to yourself, and there are entries here. I'm just looking down through it. It's D, DT, DDL, DDD and so on, and some of them are blank. Where there are blanks,

Page 96

what would that signify, do you know?

DR. MULLEN:

A. That I did--if I recall, I did not receive the slide for that case.

COFFEY, Q.C.:

Q. Okay, and I'll be--yes, because there are some here that, as we go further out through the MSH review, there are just, the row is blank.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. And I'll be taking you to that. So although there is a reference in, for example, in a specimen number -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. - for that particular patient, you, at least, in your review of the slides, couldn't find corresponding slides?

DR. MULLEN:

A. That's correct. So did you want me to continue across?

COFFEY, Q.C.:

Q. Yes, if you could, please?

Page 97

DR. MULLEN:
A. The ER, again refers to the estrogen receptor and that is the percentage of cells that were positive.
COFFEY, Q.C.:
Q. Okay, and that, I take it, is you looking -
DR. MULLEN:
A. Me looking at the original material.
COFFEY, Q.C.:
Q. The original slide?
DR. MULLEN:
A. Yes, the original slide. Now if you look down 000, 1-2-3-4-5-6-7-8-9-10-11-12, you can see the twelfth one, so the first blank and then two more, three more rather, you can see 0/0. There, I would have had two slides and so I was getting independent interpretation of both slides. So they were both submitted with the same specimen number and the same block number, but 0/0 referred to separate interpretations.
COFFEY, Q.C.:
Q. So that would be actually two separate slides?
DR. MULLEN:
A. Yes, and then the next--well, when we go to

Page 98

PR, you notice I didn't receive a PR slide.
COFFEY, Q.C.:
Q. A corresponding PR slide
DR. MULLEN:
A. PR slide was not--okay, and then if you move down to this line where the RE425, is that showing as I go across?
COFFEY, Q.C.:
Q. Okay, just a second now. Yes, RE425 is there on the screen, yes.
DR. MULLEN:
A. Yes, here, we would have two slides, 10/--the first one interpreted as 10, second is two, and then the PR, the first, I believe it would be the--I'm not sure if I could tell in each case whether it was 10 and 70 and two and 30 or would have been 10 and 30, if they're matching. But anyways, one would be 70, the second would be 30. The assessment of internal controls, again, independently for one slide, second slide and then the fixation process independently for that pair of slides.
COFFEY, Q.C.:
Q. Okay.
DR. MULLEN:

Page 99

A. So that's that, I think that was the majority of--I don't think there was any that I had more--or even if I had three, it would be 10/2/whatever, okay. Then the PR column refers to my interpretation of the original material, the progesterone receptor percentage positivity.
COFFEY, Q.C.:
Q. On the original PR slide?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. Created in Newfoundland?
DR. MULLEN:
A. Yes, provided by Newfoundland to me. The IC refers to the presence or absence of an internal control, again on the slide provided to me that was prepared in Newfoundland. So here, the first would be present and stained, absent, present stained, present, the same and then present stained weakly. So those were the three--sorry, the four present, absent, present and stained, present stained weakly, the four options that I had before.
COFFEY, Q.C.:

Page 100

Q. Now in terms of that, would this be the internal control for the ER slide, the internal control for the PR slide or both or how would that -
DR. MULLEN:
A. I would--for the internal control, my default was always to the estrogen receptor. If it were present, it refers to that. If it wasn't present, I would make--and the PR were positive, I would say the--if you look over in the comment, the ER internal control was negative.
COFFEY, Q.C.:
Q. Okay.
DR. MULLEN:
A. In this case, the present stain weakly, that was referring to the PR column.
COFFEY, Q.C.:
Q. Okay. Here is an example here, just looking at this, we'll look at the first row on the first page. In terms of that you've got ER zero, PR 70, IC, internal control, PS, which would be present and stained, F/P, which is A which I take is adequate?
DR. MULLEN:

Page 101

A. Yes.
COFFEY, Q.C.:
Q. And then if you come out further, we still have to--I'll do those in a minute, but in the comments column you've got "MSH discordant." You've noted here "ER IC."
DR. MULLEN:
A. There should be a negative there.
COFFEY, Q.C.:
Q. Okay.
DR. MULLEN:
A. I'm sorry, my apologies.
COFFEY, Q.C.:
Q. Okay. ER IC negative. And, in fact, looking at these sometimes these can be stretched out or narrow, can't they?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. And something gets cut off as you go. So we'd actually have to have the electronic spreadsheet in front of us to actually see the words?
DR. MULLEN:
A. Yes.

Page 102

COFFEY, Q.C.:
Q. Because it's written all the way out. Okay, I'm sorry, Doctor, you were about to go into--you had gotten as far as the IC column.
DR. MULLEN:
A. Okay. The fixation and processing, again, adequate or poor. Again, the criteria were set very low, was there tissue on the slide that I could interpret, that would be considered adequate unless it was, like, one or two cells and then it would be poor or very low.
COFFEY, Q.C.:
Q. Very low?
DR. MULLEN:
A. Low standard to accept as adequate. Again, I -
COFFEY, Q.C.:
Q. You were setting in this context a low standard?
DR. MULLEN:
A. Yes, extremely low standard for both the retrospective review that we discussed yesterday and this review. It's a standard that, very--as I mentioned yesterday, it was

Page 103

basically, is there anything there that I can interpret with comfort, and that's a moving target but given the size of the original section of the H&E section, given what I perceived to be the tumor, given what I perceived to be the internal control, is there enough there on the ER slide and the PR slide that, as we discussed yesterday, we prepared and that we're discussing today that were prepared in Newfoundland, is there enough there that gives me reasonable comfort that I can make an interpretation. Again, this is all material that was--that I can't go back, I can't change anything after case one. It's not something, it's not a prospective, it's all retrospective, so.
COFFEY, Q.C.:
Q. And -
DR. MULLEN:
A. Then the next, the external control -
COFFEY, Q.C.:
Q. In C column, yes.
DR. MULLEN:
A. Okay. If you look, as we go down -
COFFEY, Q.C.:

Page 104

Q. There's an awful lot of blanks.
DR. MULLEN:
A. Yes. A lot--external controls are, I believe--well, we run them once, basically, with each batch of the stain, so we wouldn't have them necessarily tagged to each case. And they may--if Newfoundland were doing cases for the other--I should say, not Newfoundland, St. John's were doing cases for Clarenville or Carbonear or Corner Brook, etcetera, they would--they may have sent the external control to them for their interpretation or their comfort. But when they were available, again, P was poor. Let's see, what do we have? I'm sorry. Can I check my -
COFFEY, Q.C.:
Q. Yes, you can. Bring up, please, Exhibit 1840, please?
DR. MULLEN:
A. I got too many Ps and As.
COFFEY, Q.C.:
Q. Page 3, please. Here you go.
DR. MULLEN:
A. What did I say?
COFFEY, Q.C.:

Page 105

Q. And EC is further down.
DR. MULLEN:
A. Oh, sorry, okay.
COFFEY, Q.C.:
Q. External control slides when available -
DR. MULLEN:
A. P for positive, query P for questionable, okay, all right.
COFFEY, Q.C.:
Q. And I'll be taking you through those, so that was just to remind yourself there?
DR. MULLEN:
A. Yes, positive--yes. I've got a lot of--P for positive, then query P for questionable. Theoretically there should be no negative, so.
COFFEY, Q.C.:
Q. And then we go on further, we go back then to NL--I'm sorry, 1837, go back up to the top of the page there, we see "NL original."
DR. MULLEN:
A. Okay.
COFFEY, Q.C.:
Q. Newfoundland and Labrador original. And a column entitled "ER" and a column entitled "PR." Now, in some instances there are

Page 106

letters or symbols or numbers?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. There. Where did the info come from and what does it mean?
DR. MULLEN:
A. In a certain proportion of cases I was provided with the surgical pathology report. These tended to be cases from the St. John's area. And on the--on some of the pathology reports I was able to, able to review what the original report for the estrogen receptor and progesterone receptor status was. In some cases, for example, use the first one, ER was reported as negative. Now, this was 1997, so I'm not sure what a negative is, whether it was less than 30, less than ten or less than one, so I put it in as an N. If there was a-- so that would be a qualitative result, and that's up to you to correlate with what the status was at that time. I didn't have any-- there was no saying--there was no--if you recall from our synoptic reports, we say what we interpret as a positive. So for each

Page 107

report there was no key or grid to what a negative meant, what a positive was. And in some cases, as in this one, the PR report-- sorry, the PR value was given numerically. In this case in '97 it was zero and zero, here we have an ER less than five but we had no PR report. And this--sorry. So we're going -
COFFEY, Q.C.:
Q. So if we could just go up to the top again?
DR. MULLEN:
A. y
COFFEY, Q.C.:
Q. So the first one, first row, the particular patient was ER, it was reported in the original Newfoundland report as a negative?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. Which you recorded here as an N?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. But as well the PR was reported as a 90?
DR. MULLEN:
A. Yes.

Page 108

COFFEY, Q.C.:
Q. Which would be 90 -
DR. MULLEN:
A. So that would, whichever threshold they were using, that would have been considered positive.
COFFEY, Q.C.:
Q. Yes.
DR. MULLEN:
A. And then the next--sorry, if we go down, this one was an oddity. This was a biochemical assay, so it would be negative and equivocal. This would be the Ligand binding assay. There would have been a hangover--not a hangover, whatever you want to call it, a hold over from the original testing.
COFFEY, Q.C.:
Q. And in terms of this, you, in referring to the biochemical assay results here, okay, you'd be doing so based upon the original pathology report in Newfoundland -
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. - which had been provided to you?

Page 109

DR. MULLEN:
A. Yes, that's correct.
COFFEY, Q.C.:
Q. Okay.
DR. MULLEN:
A. And then if we go down, Newfoundland, the result was from the Mayo Clinic, I'd make note of that. This one had little tissue on slide. And then my--so those are -
COFFEY, Q.C.:
Q. The sort of comments as we go down through the comments column, I'm not going to take you through every comment here in the comments column.
DR. MULLEN:
A. No, but -
COFFEY, Q.C.:
Q. But you would note in the comments column something, any pertinent observation, I take it?
DR. MULLEN:
A. Yes. Now, the MSH discordant, if the original--I shouldn't say the original pathology report. If the pathology report that was provided to me had my interpretation

Page 110

of the retro review, so those are the blocks that were sent to Toronto to the Mount Sinai that we stained and I interpreted, if they had reported the result to the clinician and provided it on the report, I would look at that report and say whether it was discordant or concordant. So discordant, so basically, and I don't have, I don't have the exact results here, this one if PR was 70 and ER was zero, and ER, the original was negative, the-- I would say, I would think that we can check the--we'd have to go to check the two spreadsheets, that my ER that I reported in Toronto would probably be positive. And based on the fact that I have a very strong PR, chances are that ER would probably also be positive. And the discordant would be if it changed, basically if it changed categories. If it were zero or less than one and I changed it to anything greater than one, one to ten or ten or above, that I would call discordant, anything basically that I thought would indicate a change that might indicate a change in therapy.
COFFEY, Q.C.:

Page 111

Q. And that would be you, in terms of recording something as discordant in the comments column, it was based upon the pathology report from Newfoundland that you received in 2008, you would read it?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. If there was some reference to the retrospective results done by Mount Sinai recorded there, you'd look at that, the figures there, and compare that to the original pathology numbers or commentary, whatever it was, and make a determination yourself as to whether you thought your results, if they were reflected in the pathology report, were discordant with the original pathology report?
DR. MULLEN:
A. Yes, that is correct. And again, when I used my categories, they were based on the current practice at the Mount Sinai for therapy.
COFFEY, Q.C.:
Q. For therapy.
DR. MULLEN:

Page 112

A. I did not go back to the original spreadsheet to look, like the 500 cases, that was sort of out of the scope of this review.
COFFEY, Q.C.:
Q. To actually check to see?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. For example, you didn't go back to check against your original spreadsheet reports to see if on the actual pathology report St. John's had actually recorded it correctly?
DR. MULLEN:
A. Correct.
COFFEY, Q.C.:
Q. You didn't cross reference that?
DR. MULLEN:
A. Yes. And the ones that I didn't have, I didn't fill in. That was--this was time limited and -
COFFEY, Q.C.:
Q. So if we could, Doctor, what I'd like to do, please, is look at Exhibit P-1840, page 3, please? Thank you. And just to run down through this, Doctor, the MSH data spreadsheet

Page 113

code, MSH review. If we could, just up there, the tumor type, these, again, this code for tumor type we've seen before in the retrospective?

DR. MULLEN:

A. Yes. And when I was looking at the, reviewing this last night, there's one that I didn't have in here, "NT" there should be an "NIT" no invasive tumor. So after the processing for the ER/PR I lost the invasive component or there was no invasive component left, there was only ductal carcinoma in situ or there was no tumor at all. And there's a new term here that we didn't have in the previous case, and that's called lymphangitic carcinoma, which is basically the presence of tumor in lymphatics rather than an invasive component.

COFFEY, Q.C.:

Q. And there's at least one such case?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. In this, these 539 or so?

DR. MULLEN:

A. Yes. And then the -

Page 114

COFFEY, Q.C.:

Q. The number here.

DR. MULLEN:

A. Which we didn't have before, no H&E, no routine slide to assess tumor, and there was no tumor present in the ER/PR slide, so.

COFFEY, Q.C.:

Q. And under "ER" you have percentage cells positive, that is looking at the original ER slide?

DR. MULLEN:

A. Yes, that is again my interpretation of the original slides provided by Newfoundland.

COFFEY, Q.C.:

Q. And PR, same thing?

DR. MULLEN:

A. Same, same.

COFFEY, Q.C.:

Q. The IC here you've written here, "Internal controls with P present but not stained. PS present and stained. PSW, present and stained weakly. A for absent. The value refers to the ER internal control. If the ER and internal control was not present within the-- was not present within, the value refers to

Page 115

the PR internal control?

DR. MULLEN:

A. Yes. I think the "and" should be dropped.

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. If the ER internal control was not present within that section the value refers to the PR.

COFFEY, Q.C.:

Q. Yes. So if the ER internal control, that word "and" shouldn't be there. "If the ER internal control was not present within," that's within the slide?

DR. MULLEN:

A. With that section, yes.

COFFEY, Q.C.:

Q. The value refers to the PR internal control, that is the value in the IC column?

DR. MULLEN:

A. Yes, that's correct.

COFFEY, Q.C.:

Q. The comment in the latter case will state "ER IC negative," in other words, estrogen receptor, internal control, negative?

Page 116

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. And that would be out in the comments column?

DR. MULLEN:

A. That was in the comments.

COFFEY, Q.C.:

Q. "F/P," fixation and processing with A for adequate and P for poor." "EC" under that column "External control slides, when available," with a P, indicating positive. Question mark P, questionable positive. If both ER and PR external control slides were present, they were reported as P/P. If only the ER control slide was present, it was reported as "P". If only the PR control slide was present, I'm sorry, it was reported as slash, P. And if two sets of control slides were present, they were reported as "P/P/P/P." No external control was negative. What internal controls--external controls were there?

DR. MULLEN:

A. Yes. The -

COFFEY, Q.C.:

Page 117

Q. The slide review, they all -
DR. MULLEN:
A. Well -
COFFEY, Q.C.:
Q. - were positive to some extent?
DR. MULLEN:
A. Positive or -
COFFEY, Q.C.:
Q. Or questionable positive?
DR. MULLEN:
A. There were a few that were questionably positive. And under the heading "NL original" the column ER and, the columns ER and PR, the results present on the accompanying--"The results present, on the accompanying report," that is the surgical pathology report, I take it?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. When provided to you, "If a numerical value was not reported, then the qualitative result was entered" N for negative, MP for moderately positive, WP for weakly positive, OP for occasionally positive, and rare, r-a-r-e, for

Page 118

rare positive. Now, these terms, I'll just ask you now, the idea of using the phraseology "rare positive" or "occasionally positive" I take it that's just what was in the -
DR. MULLEN:
A. That was in the report.
COFFEY, Q.C.:
Q. And if it was there, that's the code you used?
DR. MULLEN:
A. Yes, yeah. Basically what I was doing was trying to group the reports. If there was a quantitative value, that was put in; if there was a qualitative, these were the terms that were used, negative, moderately positive, weakly positive, occasionally positive and rare, rare positive. I'm not sure, again, what the cut offs were, what they mean.
COFFEY, Q.C.:
Q. Here you conclude in that particular category here by saying "One PR result measured by biochemical means was reported as E for equivocal"?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:

Page 119

Q. Which is you just referred the Commissioner to that, that -
DR. MULLEN:
A. That's the Ligand binding assay.
COFFEY, Q.C.:
Q. Yeah.
DR. MULLEN:
A. I believe it was Ligand binding assay.
COFFEY, Q.C.:
Q. Here then under the heading, or the column entitled "Comment" you've written "When a surgical pathology report was provided which included the results of the MSH retrospective review, I compared the NL results to the MSH results. The results were categorized as concordant if the two results were in the same ER group and discordant if they were in different ER groups." And it's "(Negative being less than one percent, low positive being one to ten percent and positive being greater than ten percent)."
DR. MULLEN:
A. That's correct.
COFFEY, Q.C.:
Q. And, doctor, just to--without having all of

Page 120

these, what original--I'm sorry, what pathology reports, surgical pathology reports you did receive from Newfoundland in the course of the slide review, the slides themselves and the pathology reports were sent back to Newfoundland?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. Okay.
DR. MULLEN:
A. Everything, if you remember the cover letter, everything was returned to you. Sorry, returned to the Commission of Inquiry.
COFFEY, Q.C.:
Q. If we could, and this may--and I've just, I've picked two examples of something. If we could look, please, at, on this exhibit, 1837, look at, please, page 7? I'm just going to, if we could, come down toward the bottom of the page and--across here. And look at what is identified as number in the left-hand column, 659? Thank you. Go back a bit further. 659, come across, and it's surgical number SS4 -
DR. MULLEN:

Page 121

A. 4457.
COFFEY, Q.C.:
Q. - 547. The year is indicated to be 2000, the block is indicated to be A2. Just go across here now.
COMMISSIONER:
Q. So, seventh up from the bottom?
COFFEY, Q.C.:
Q. Yes, that's correct, Commissioner. Sorry. Look at the block there, it's A2. And coming across under the column H&E which would be D for ductal, as would -
DR. MULLEN:
A. Yes, using the code, yes.
COFFEY, Q.C.:
Q. The code. The ER under the column "MSH review" you categorized what you were seeing on the ER slide as a -
DR. MULLEN:
A. Five.
COFFEY, Q.C.:
Q. Five percent?
DR. MULLEN:
A. Um-hm.
COFFEY, Q.C.:

Page 122

Q. And the PR slide as 20 percent?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. Under the internal control you've indicated as A for absent?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. At least on the slide, the original slide you were looking at. The F/P, in this context I believe is adequate?
DR. MULLEN:
A. Adequate, yes.
COFFEY, Q.C.:
Q. And -
DR. MULLEN:
A. That's the external controls present for both ER, present for both PR.
COFFEY, Q.C.:
Q. Yes. And then we come over -
DR. MULLEN:
A. That's right, sorry, yes, positive.
COFFEY, Q.C.:
Q. And under the Newfoundland original - in

Page 123

looking at the Newfoundland pathology report, the ER again reported, you know, here as five.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. And the PR as 30 to 35.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. And you've noted it to be Mount Sinai discordant.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. And in terms of that - and we'll just look at the five here and the five here.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. Following the cursor - so, of course, they're the same figures.
DR. MUNDEN:
A. Yes, I agreed with their original interpretation.
COFFEY, Q.C.:

Page 124

Q. The interpretation in the sense of the percentages.
DR. MUNDEN:
A. Yes. Yes.
COFFEY, Q.C.:
Q. For ER.
DR. MUNDEN:
A. Based on the material provided to me, I would have assessed that case as having five percent positive. The Newfoundland report had five percent positive. The PR, I said 20. It was reported as 30 to 35. For all intents and purposes, they are the same category. So ER is low positive in both cases. PR is positive in both cases.
COFFEY, Q.C.:
Q. Now if we could, please, bring up Exhibit P-1811. Now this we've looked at yesterday, doctor. This is your e-mail of January 20, 2006, sending what is a spreadsheet of what was then thought to be the completed ER/PR results for the retrospective review conducted by Mount Sinai.
DR. MUNDEN:
A. Yes.

Page 125

COFFEY, Q.C.:
Q. If we can go to page 3, and here we come down the left-hand side and you will see - and I haven't counted it up, Commissioner--if somebody wants to, they're certainly welcome to. Under the specimen number - and the cursor is pointing--well, I had it pointed there - it's SS4547. It's 00SS4547 and, if anybody wants to, they can turn back to Exhibit P-1837, Page 7, and they will see that that's the same specimen number we were just looking at. That's 7 from bottom on Page 7. Okay, if we can go back then to - okay, P-1811, thank you - and here 4547, we come across -
DR. MUNDEN:
A. Block A2.
COFFEY, Q.C.:
Q. It's at Block A2. The comments - it came from St. John's, identified as coming from St. John's. The tumour is indicated in your report of January 20th, the spreadsheet of January 20, 2006. As the report said, the tumour is a "D" for ductal. Here you've reported the ER as 90, which would be 90

Page 126

percent?
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. And you've reported the PR as 80 percent.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. And the internal control - that is the one -
DR. MUNDEN:
A. It would be -
COFFEY, Q.C.:
Q. - looking at the slides in Mount Sinai -
DR. MUNDEN:
A. Yes, a re-stain of the original block.
COFFEY, Q.C.:
Q. Yes.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. Present and stained.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. And F/P is adequate.

Page 127

DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. So I take it then, doctor, that it's your view that you're having reported - and I presume that this 90 and 80 must have been reported for this particular patient on their surgical pathology report.
DR. MUNDEN:
A. Based on my key and based on the fact that I said that they were discordant, it would be logical to say that, yes, they were on the report.
COFFEY, Q.C.:
Q. On the report.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. Because you didn't actually go back to the original spreadsheets -
DR. MUNDEN:
A. No. I had a time limit to have this done and back because I believe there was some other activity with these slides, so I didn't have the time to do that.

Page 128

COFFEY, Q.C.:
Q. Now here, if indeed that 90 and 80 do appear -
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. - on the surgical pathology report related to this particular patient, then the 90 and 80 would be discordant with a report of -
DR. MUNDEN:
A. Five and 30 - 5 and 20 or 5 and 30 -
COFFEY, Q.C.:
Q. Five and 30 to 35.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. Okay.
DR. MUNDEN:
A. Discordant in the sense that low positive to a very high positive.
COFFEY, Q.C.:
Q. Yes, and there's a big jump from 5 to 90, I take it.
DR. MUNDEN:
A. Yes.

Page 129

COFFEY, Q.C.:
Q. In your world.
DR. MUNDEN:
A. Yes, that's a significant difference and the response to therapy would be--the anticipated response to therapy might be quite different.
COFFEY, Q.C.:
Q. Well, one other now while we have up this page - if we could look at the specimen number in a left-hand column on Page 3 of Exhibit of P-1811, SS6349 - see that 6349 here?
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. Okay.
DR. MUNDEN:
A. Block D?
COFFEY, Q.C.:
Q. From across from Block, D it's ductal and it's reported as here in January of 2006 in the spreadsheet Mount Sinai has reported it as 90 for ER and zero for PR.
DR. MUNDEN:
A. Yeah.
COFFEY, Q.C.:

Page 130

Q. And the internal control is present and stained and "A" for adequate fixation/processing.
DR. MUNDEN:
A. Uh-hm.
COFFEY, Q.C.:
Q. And if we could, please, go to Exhibit P-1837, Page 8, please, and if we come down -
DR. MUNDEN:
A. Six - oh yes, there we are.
COFFEY, Q.C.:
Q. The sixth row, we will see a specimen number and the specimen number is 00SS6349.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. And your specimen is 2000. It's Block D.
DR. MUNDEN:
A. It's coming across here.
COFFEY, Q.C.:
Q. The H&E in the MSH review of the slide review conducted, reported in your view to H&E as "D" for ductal. The ER is zero. The PR is zero. The internal control is present - "P" meaning present.

Page 131

DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. But it's not stained - at least that's correct.
DR. MUNDEN:
A. That's correct.
COFFEY, Q.C.:
Q. And looking back at your key, that would mean the ER internal control was present but not stained.
DR. MUNDEN:
A. That's correct.
COFFEY, Q.C.:
Q. F/P is marked with an "A" for adequate and, in looking at the Newfoundland report, you had noted there that--in reading it, the original pathology report indicated--recorded as "N" for negative.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. For ER, and "N", a negative for PR.
DR. MUNDEN:
A. Yes.

Page 132

COFFEY, Q.C.:
Q. And you've noted this to be Mount Sinai discordant.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. So I take it, doctor, that here if indeed the pathology report, when you looked at it, contained the Mount Sinai results.
DR. MUNDEN:
A. Yes, there's a significant difference between -
COFFEY, Q.C.:
Q. Well, negative, I take it, and 90.
DR. MUNDEN:
A. Ninety, yes - there is a significant difference and with implications for therapy.
COFFEY, Q.C.:
Q. Because though Mount Sinai had said here - and we look back at P-1811, please, Page 3 - yes, so we have it. Thank you, Registrar. Even though here looking at this, the ER is 90 and the PR is zero.
DR. MUNDEN:
A. Yes.

Page 133

COFFEY, Q.C.:
Q. And the original pathology report had indicated it was "N" for negative for PR which would be concurrent with your review.
DR. MUNDEN:
A. Negative for both, I believe, yes.
COFFEY, Q.C.:
Q. Yes, but -
DR. MUNDEN:
A. Oh sorry, the PR, yes. Yes, I -
COFFEY, Q.C.:
Q. The PR was fine, I take it, in terms of concordance.
DR. MUNDEN:
A. Yes, in the sense that whatever I was interpreting it as zero - zero can be negative.
COFFEY, Q.C.:
Q. Yes.
DR. MUNDEN:
A. Less than 10 or less than 30, depending on their cut points at that time, but I was -
COFFEY, Q.C.:
Q. but if "N" meant negative -
DR. MUNDEN:

Page 134

A. Yes.
COFFEY, Q.C.:
Q. And was negative recorded there, and you had recorded it as zero and zero would certainly be negative.
DR. MUNDEN:
A. Yes.
COFFEY, Q.C.:
Q. But in terms of the ER for this particular patient, St. John's you've noted here - in its original pathology report, it's recorded this particular patient's sample as "N" for negative for ER.
DR. MUNDEN:
A. That is correct.
COFFEY, Q.C.:
Q. And 2006, certainly, you had reported as 90 percent positive for ER.
DR. MUNDEN:
A. That is correct.
COFFEY, Q.C.:
Q. If we could look, please - and I guess this is another topic. It's something I did want to visit though before concluding with you, doctor, although I'm not quite there yet.

Page 135

Exhibit P-1838 - this, doctor, is labelled Newfoundland ER/PR flow-chart. Have you seen this before?
DR. MUNDEN:
A. Can I see when it was - sorry, the date, I'll go to the bottom.
COFFEY, Q.C.:
Q. Sure.
DR. MUNDEN:
A. No, there is no date on it. Okay, this would have been prepared some time after the beginning of--in at least April of 2007 because Newfoundland had repatriated the ER/PR and we were just doing QA's after March--I think it was March 17th? Sorry, I don't have it.
COFFEY, Q.C.:
Q. So the flow-chart, I take it is--
DR. MULLEN:
A. It's for the technical--it's for the handling of the specimen.
COFFEY, Q.C.:
Q. To kind of keep track of how things should flow, I take it.
DR. MUNDEN:

Page 136

A. Yes.
COFFEY, Q.C.:
Q. From Mount Sinai's perspective.
DR. MUNDEN:
A. Yes. Okay.
COFFEY, Q.C.:
Q. Okay, so that's -
DR. MUNDEN:
A. So do you want me to take you through it or -
COFFEY, Q.C.:
Q. If you would, please, yes.
DR. MULLEN:
A. Okay. So we have currently three types of specimens that we are receiving at the Mount Sinai Hospital, so all sites in Newfoundland. There are the ER/PR retrospective cases. These are the cases that are a follow-up to the original review. So all of the blocks from '97 to 2005 - these, I believe, are blocks from patients that have requested a repeat analysis. They may have been positive called in Newfoundland or negative. I believe they're mostly positives, and I'm repeating them at the patient's request through the clinician or the pathologist. So that would

Page 137

be that retrospective group. The ER/PR QA, that was active from--it would have been April 2007 to probably - well, I think we'd probably have it on hold at the moment - to June 2008. These are cases that--really, they're actually blocks that are submitted to the Sinai for re-staining and interpretation and returned to Newfoundland on a spreadsheet, as are the first ones on a spreadsheet. This is quality assurance. They are having the staining repeated. They were having the staining repeated at the Mount Sinai Hospital and comparing it to the stains that were being done in Newfoundland. And then the third category, Newfoundland consults, these are cases, the prospective that we started in August of 2005. It's a continuation of that. So those would be the ER/PR and the HER2, any combination or permeatation of that group. So either ER/PR and HER2 or ER/PR or HER2, so that's that group, and then this is basically how we fill out the form. The QA request comes and then the retrospective request form - they're put together. This is for Newfoundland and they're mailed to who

Page 138

receives them in the lab. So because these are not part of what we consider the service component and part of the research services area of the department, they're handled by Maria Mendes and Mona Reid, head of the Special Services and the technologist assigned to QA.

On the other side, this is we're asking for--because they're consultations - if you recall the letter that we had to Dr. Dankwa as the template, it's basically a continuation of that form. We'd like a cover letter telling me what breast or the pathology report and they're mailed and they're handled as a consultation. So basically they're--and part of it is the type of form, I will issue a formal report that I then fax to the hospital. It expedites the reporting of the case. And the turn around time was like two or three days on most of these cases.

COFFEY, Q.C.:

Q. Okay.

DR. MULLEN:

A. Now, I believe there's another sheet with this or is that it? Okay. So the retrospective

Page 139

are the continuation. And if Newfoundland finds more cases that were initially missed, it's that group or the patients who have concerns and we're reconfirming their results.

COFFEY, Q.C.:

Q. Okay.

COMMISSIONER:

Q. So I take it the origin or the type of case which had been sent to you determines into which stream within Mount Sinai something flows?

DR. MULLEN:

A. Yes, that is correct. And the consequence of that is the type of report that is issued and the billing procedure.

COMMISSIONER:

Q. Billing.

DR. MULLEN:

A. One is billed to the heath, MCP and the other is billed to the hospital.

COMMISSIONER:

Q. All right.

DR. MULLEN:

A. The same, the same service is provided to

Page 140

both. They're both stained the same way and etcetera.

COMMISSIONER:

Q. Um-hm.

DR. MULLEN:

A. It's just the type of report. And the QA is an internal document for the department and the retro is for them to deal with.

COMMISSIONER:

Q. Okay.

COFFEY, Q.C.:

Q. Doctor, statistics, for example, positivity rates for ER and PR.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. I'll just ask you do you, in your own practice, do you keep track of your own statistics?

DR. MULLEN:

A. Yes, rigorously.

COFFEY, Q.C.:

Q. Okay.

DR. MULLEN:

A. Yes.

Page 141

COFFEY, Q.C.:
Q. Would it be fair if I was to ask you is that something limited to yourself or peculiar to yourself or is it universal or is there something in between?
DR. MULLEN:
A. Something in between.
COFFEY, Q.C.:
Q. Okay. Perhaps you could elaborate on that?
DR. MULLEN:
A. Okay. As we were going through my CV you notice I have a background in mathematics, so I like playing with numbers or driving numbers. So and I also I'm quite comfortable using our lab information system. I'm also a titch obsessive/compulsive so I report everything the same way. I cut and paste. So we have a fairly good lab information system, but it has a few deficiencies. So it can only search certain areas, it can search clinical history and it can search diagnosis. So since I've been doing Newfoundland and when I'm doing Newfoundland and also the consultation services in Ontario, I basically, to speed things up, I cut and paste. I have templates,

Page 142

I cut the report and stick it in. So all of my estrogen and progesterone--all of my breast cases are signed out exactly the same way. It'll be positive for estrogen receptor protein, negative for estrogen receptor protein, positive, open brackets, low, whatever. And the same for progesterone and then the HER2. So I do, I can do a search on positive for estrogen and under my name everything that I've signed out and I can do it from any time frame, any time it's accession, any source. So I run those every six months or so. And I--and when you presented to Toronto, I think I provided you with--I don't know if I mentioned this yesterday, my concern was not knowing what the material was, what my positivity rate as compared to the literature and I was quite off on the retro review, which is the material that was stained in Toronto. And to ground myself and to convince myself that I actually knew how to sign these things out, I had done the--I compared it to the prospective material from Newfoundland the same time, I compared it to a series of regional hospitals that refer

Page 143

to us that I had signed out during the same time frame, well, they started in '06 rather than '05, and then I compared it to all my material. So I had all of that, my ER positivity rate, just--and then in preparation for this appearance I've done my ER--I've done the four categories, ER positive, PR positive, ER positive, PR negative, sorry, ER negative, PR positive, and ER negative, PR negative. So I have all of that data from basically the beginning of '05 to the beginning of--to the beginning of June, I didn't--the first week in June. The last cases from Monday I didn't include into this. The other issue is that I have done enough of these cases, and sorry, the statistics I'm going to give you or discuss, I have not included the retro review.
COFFEY, Q.C.:
Q. Yes.
DR. MULLEN:
A. That's -
COFFEY, Q.C.:
Q. Because I take it that was the -
DR. MULLEN:
A. That would skew everything.

Page 144

COFFEY, Q.C.:
Q. Because it was a very -
DR. MULLEN:
A. It was a selected group.
COFFEY, Q.C.:
Q. Selective group?
DR. MULLEN:
A. Yes. So they weren't in. But I did include the prospective from Newfoundland because I think those were legitimate to include. So I have--I mean, to do statistics or to--if you have ten cases, it's hard to say what your positivity rate of, you know, seven, that 70 percent or six, is that a major deviation. Once you start to get up into the thousands, like I'm just trying to think--so basically from the beginning of '05 to June of '08 I have 1439 cases, so I think that gives me robust enough numbers to do statistics on. And my category--my statistics, can I recall the nurses' study for you? Did Frances O'Malley speak about the nurses' study, the expected positivities? Oh, she -
COFFEY, Q.C.:
Q. I think she may have in passing but -

Page 145

COMMISSIONER:
Q. She didn't refer to it as the nurses' study.
DR. MULLEN:
A. Oh, sorry.
COMMISSIONER:
Q. I don't remember her referring to it as the nurses' study.
COFFEY, Q.C.:
Q. She may have used the actual service -
DR. MULLEN:
A. Yes, she may have the actually--I can pull out the report if you like. Sorry.
COMMISSIONER:
Q. Okay.
DR. MULLEN:
A. So the nurses' study, wish I had a blackboard, but anyways, ER positive, PR, it was the nurses' study of 2096 cases of breast cancer. The ER positive, PR positive, they had 1281, which is 61.2 percent were positive for both. ER positive, PR negative they had 318, which is 15.2 percent. ER negative, PR positive, they had 80 cases, which was 3.8 percent, and ER negative, PR negative, they had 19.9. So at the bottom--so to round things off, about

Page 146

76 percent should be, well, 76.4, to be exact, should be ER positive, another approximately 3.8 percent should be PR positive, and then about 20 percent should be ER/PR negative. So I would be aiming for that ball park. So if I looked at the--when I presented my data in December, I just looked at the ER positivity, I didn't break it into the four groups at that time in December, so beginning of '05 to December, which includes the Mount Sinai internal cases, which proportionately would be very small compared to Newfoundland and my--the other consults I get, because I would be dividing that service. I do the majority of the ER/PR and consult work. I had 1133 cases and my PR--my ER positivity was 77.2 where the literature says I should be 76.4, so I didn't think that was too bad. And my, Greater Niagara, which is a, I believe three or four hospitals would be analogous to the Newfoundland situation where we have different hospitals processing the tissue, sending it, then they send it to the Mount Sinai, they don't do anything directly, send it to Mount Sinai, they were 79.4 percent positive. And

Page 147

Newfoundland, I had 236 cases that were--and 79.2 percent. So the Newfoundland go forward or the Newfoundland perspective--prospective were in the right ball park. So to update -
COFFEY, Q.C.:
Q. The go forward current cases?
DR. MULLEN:
A. Yes, prospective from August, ''05 to, that time is December, beginning of December, '07.
COFFEY, Q.C.:
Q. Okay.
DR. MULLEN:
A. So in preparation for this I did the '05 to basically the end of the first week of June. And I had done, by that time, 1439, so another basically 300 cases in five months or six months. I broke it down better here. My ER greater than ten and breaking it down were 78 percent and my PR positivity rate was . 5 percent, so 78.5 percent. So that was--and my expected should be basically 80, so I'm in the 70--sorry, 80 percent. So I'm in the--two percent off, which I don't think is too bad.
COFFEY, Q.C.:
Q. Doctor, when you say ER positive, the cut off

Page 148

for that positive is?
DR. MULLEN:
A. I added both, I added the greater than ten and greater than one.
COFFEY, Q.C.:
Q. Okay.
DR. MULLEN:
A. And greater than ten, if you remember the literature or you know the literature better than I do after discussing things with you, there's basically a dichotomist situation, you're either completely negative or greater than 70 in almost 90 percent of--over 90 percent of cases. There are very few that are in the less than 70. So my ER that I had between one and ten were only 11 cases, which would be one one hundredth, one percent of my cases. So basically 78 percent were positive and the PR, this I have to look at, is only .5 whereas the literature says about 3.8. So I might be slightly over calling the ER and under calling PR, but that's the--I am in the ball park.
COFFEY, Q.C.:
Q. Okay. And now in terms of the statistics

Page 149

themselves, though, I take it you utilized them just, I take it, like, as you say, about every six months or so you go and run your stats and have a look back. But I'm just going to ask you about the utility of statistics themselves. In the context, Doctor, of the day-to-day work of a pathologist in the sense that if you were relying solely upon statistics to determine from day to day whether or not you were diagnosing or reporting a case properly, I take it that you could go quite a period of time before the statistics would show you that you were over or under, over or under calling something?

DR. MULLEN:

A. Yes. I mean, statistics are great when you want to show how productive you are and how you fit into everything, but as I was trying to mention earlier, I don't know if I was clear enough, it is the individual case that triggers the alarm. The absence of internal controls, the lobulars, the tubulars, the mucinous that are negative, that is what triggers the alarm. I don't care what my

Page 150

stats are if I have 78.5 or whatever the exact, that has no bearing on my report. It's what the individual case is. And those, any deviation from what I expect and, you know, with the positive internal controls, the tumors being positive, any deviation triggers alarms, both myself, my colleagues and our staff. So if we don't fit what we expect, we act. We don't wait for my percentage to drop to, like, 75 or whatever it is. And when you get enough cases, you need a large deviation from normal practice to pick it up.

COFFEY, Q.C.:

Q. Doctor, how long has Mount Sinai been using the one percent figure?

DR. MULLEN:

A. I believe the beginning of 2000. I believe Dr. O'Malley may have spoken that she was a participant in the study that established the one percent cutoff. We started in 2000.

COFFEY, Q.C.:

Q. How about before that, what -

DR. MULLEN:

A. I believe it was ten percent. It's always been my policy and I believe most of my

Page 151

colleagues' policy to give a numerical value as well as an interpretation because as you know the literature changes, the clinicians' practices change, so it's much easier on a go-forward basis to give as much information as possible. It's very time consuming to pick up the slides, first of all, you have to find them, they may be--that sort of thing. You give as much information going forward so that they can deal with things.

COFFEY, Q.C.:

Q. And, Doctor, just something that arose yesterday and there's some topics I want to cover with you now. I apologize if I appear to be moving between different things, to yourself and the Commissioner. But you did reference yesterday a conversation you had with Dr. Carter in November of 2005 when she was in Toronto?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. And you indicated to her, to us that you had spoken to her about concerns or problems you were observing, you know, in the Newfoundland

Page 152

material, the current Newfoundland material?

DR. MULLEN:

A. The prospective material, yes.

COFFEY, Q.C.:

Q. Prospective material. When you were speaking to Dr. Carter about that, do you recall if she said anything to you about--you know, did she make any observations in that regard?

DR. MULLEN:

A. Most of the--I mean, there were general--the conversation was general about I'm having issues, I'm doing a lot of, when I say extra work, it was referring to the HER2s that we had to go to FISH because of the--we didn't feel that the specimens were--it wasn't particular to the ER/PR, it was the general fixation processing issue. And then I, if I remember correctly, I mentioned yesterday a woman who had had bilateral breast surgery on the same day and one specimen was what I would consider adequate and the other specimen was almost uninterpretable, received the same time, removed within an hour or two of each other and path A was fairly acceptable, path B, and I asked her what conceivably could have

Page 153

happened. And she, if I remember correctly, mentioned that the--I don't think they had established a refrigerator in the operating--simple things like a refrigerator in the operating--not in the operating room, but in the receiving room, wherever, however they're set up there. And I'm not sure about their portering system and formalin. But the main thing that struck me was the absence of a fridge.

COFFEY, Q.C.:

Q. Did Dr. Carter at the time seem to you that she was aware of these sorts of issues already?

DR. MULLEN:

A. Yes, she seemed--it didn't come out in the testimony earlier, but I was--I had a few conversations with Dr. Carter over the fall and she was quite frustrated with, I don't want to put words in her mouth, but frustrated with the lack of response to her concerns, as well. I think my concerns mirrored her concerns. I believe when--I don't think there's anything that I've said that she would not have said.

Page 154

COFFEY, Q.C.:

Q. I'm sorry, Doctor?

DR. MULLEN:

A. I'm sorry, I think my concerns mirrored her concerns. I don't want to put words in her mouth, but I don't think I've said anything that would contradict anything that she was saying.

COFFEY, Q.C.:

Q. And in terms of, because you've mentioned the refrigerator, Doctor, is there anything special about the sorts of fridge you're talking about or is it, you know, is it just a normal refrigerator?

DR. MULLEN:

A. It's a bar fridge, basically.

COFFEY, Q.C.:

Q. Pardon me?

DR. MULLEN:

A. Bar fridge. You go to Wal-Mart and you buy a Danby, like, "foom, foom".

COFFEY, Q.C.:

Q. Okay. So this is like the refrigerators -

DR. MULLEN:

A. It's $300 at most.

Page 155

COFFEY, Q.C.:

Q. Okay. So the refrigerator in this context would be just an ordinary refrigerator?

DR. MULLEN:

A. Yes, oh, yeah. There's nothing major about this. This doesn't have to be temperature controlled, it's just something to cool the specimen. I didn't--one of the issues when you're fixing something, formalin will penetrate faster if you heat the specimen. The problem is if you heat the specimen, it'll degrade much faster. So it's--so we do formalin before it arrives in the OR, we put--arrives in the department we put it in formalin in a fridge, like a--and because it's an under counter, it's basically what I would consider a bar fridge, like.

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. I just bought one myself for sort of as a temporary thing, it's a Danby, it's less than $300.

COFFEY, Q.C.:

Q. So, Doctor, in terms of that, and the whole

Page 156

point of it, I take it, in doing so, in storing the tissue in Formalin temporarily in a refrigerator is just to keep the Formalin and the tissue cool?

DR. MULLEN:

A. Yes, you're trying to cool the--cool the specimen to slow degradation. The ideal is the minute the specimen is removed, it's brought to pathology, it's serially sectioned and put in Formalin. If that's not available, then the next best thing is in Formalin, in a sufficient amount of Formalin in a refrigerator and then brought to pathology. And ideally breast surgery is not doing at 6:00 on a Friday afternoon and sits in a fridge over the weekend, it's done, it's processed properly.

COFFEY, Q.C.:

Q. Doctor, the idea of false negatives, I'm sorry, false negatives, false positives, the concept of false positives for ER and PR, is there such a thing, a false positive?

DR. MULLEN:

A. Yes, they would be, if you have a properly validated antibody, it would be unlikely that

Page 157

you would get a false positive. False negatives would be much greater possibility. Basically what you're saying is that you're detecting something that's not there.

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. So part of it might be your, well, your threshold value if you haven't--I believe Dr. O'Malley mentioned the TMAs that we do. When we validate an antibody, the estrogen, progesterone antibody we do tissue microray and these are specimens that have been correlated with Ligand binding assay, so we do a negative, so when it was negative, a low positive and a high positive. So we, when we do our antibodies, we match the reactivity to what's the biochemical assay, so that's basically the validation. And then we--so if you are getting, I don't know how you'd do it, but if you're getting a positive on a negative and you brought that into production, then, yes, you could have a false positive. But biologically, you know -

COFFEY, Q.C.:

Page 158

Q. It would be rare?

DR. MULLEN:

A. Yes, very uncommon. Assuming you're using the right antibody.

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Doctor, in terms of the prospective, is the term you use, or current cases from Newfoundland and Labrador, you've been reporting them, the current prospective cases since August of 2005 for all of Newfoundland and Labrador outside St. John's?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. In particular. And up until March of, February/March of '07 for St. John's and you just started St. John's again?

DR. MULLEN:

A. Yes, that's correct.

COFFEY, Q.C.:

Q. Can you tell the Commissioner, please, I want

Page 159

to just explore with you two things, you did indicate in a January 20th, 2006 e-mail to Dr. Cook that there were some things you thought perhaps would be useful to discuss him, as well you had spoken to Dr. Carter back in November of '05. And your concerns were in relation to what you were seeing in the current cases then, what sorts of things?

DR. MULLEN:

A. The prospective. My concerns were basically that I was having the same sample preparation problems that existed in the retro. So whether it was--so the sample handling between the time it was removed from the patient to the time the block was prepared. So was it fixation issues or processing? And when we talk about fixation, we're talking, you know, that fridge issue would be part of the fixation issue, the transport to pathology, the serial--the sectioning of the specimen would all be part of the issues that should have been addressed. Basically the proper handling of the specimen between the time it's removed from the patient to the time I get a block, or the time the lab gets a block.

Page 160

Those are all the--there were all those issues.

COFFEY, Q.C.:

Q. Doctor, has that changed?

DR. MULLEN:

A. There has been a reduction in the issues, yes, there are still occasional cases, but over time the number has decreased.

COFFEY, Q.C.:

Q. I take it that the quality then, from your perspective, of the fixation process and the processing itself of the tissue into blocks has--what you're seeing under the microscope has improved?

DR. MULLEN:

A. Somewhat, yes.

COFFEY, Q.C.:

Q. Somewhat.

DR. MULLEN:

A. It's not, by no means is it 100 percent. I mean, we still have -

COFFEY, Q.C.:

Q. It's not as bad as it was?

DR. MULLEN:

A. No, but it's not 100 percent. It hasn't met

Page 161

the equivalent of either my Greater Niagara or my Humber River consult cases.

COFFEY, Q.C.:

Q. Okay. So, I'm sorry, could you just on that point?

DR. MULLEN:

A. That we can sit down, when we sit down to sign out the case, pick out which case, even before we look at the slides, this is Newfoundland, this is that sort of thing. They're still -

COFFEY, Q.C.:

Q. Even before you look at the slides?

DR. MULLEN:

A. Yes. I mean, as you look at--you don't pick up the requisition, you look at the slide, you see the artifacts of the tissue exploding. You know that this is going to be--there are certain places that we get that issue from.

COFFEY, Q.C.:

Q. And Newfoundland and Labrador -

DR. MULLEN:

A. There's more, there's more of them.

COFFEY, Q.C.:

Q. Yes. And you say -

DR. MULLEN:

Page 162

A. But it's not 100 percent.

COFFEY, Q.C.:

Q. When you say you look at the slides, I take it you're looking at them just gross?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Without a microscope.

DR. MULLEN:

A. Right, right.

COFFEY, Q.C.:

Q. You can even tell -

DR. MULLEN:

A. It doesn't take--you don't have to have a microscope to see that there's nothing on it.

COFFEY, Q.C.:

Q. Or there -

DR. MULLEN:

A. And pathology, remember, pathology is, from the naked eye through to--as most, the highest power you can get.

COFFEY, Q.C.:

Q. So, Doctor, in terms of that, I take it that dealing with that that there is a difference that you've--you could, if you had them here

Page 163

in front of you, different slides from different areas, different regions, not so much within Newfoundland as from different regions across the country where you're -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. That you'd be able to say, well, this looks like a Newfoundland case even just looking at the -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. - slide in a--without a microscope at all?

DR. MULLEN:

A. Right.

COFFEY, Q.C.:

Q. And you would attribute the shortcomings in that regard in respect of the product that you were seeing to fixation?

DR. MULLEN:

A. Slash, specimen handling, fixation/processing, if we include the pre placement in formalin serial section type, yes.

COFFEY, Q.C.:

Page 164

Q. Okay.

DR. MULLEN:

A. I would--I think the vast majority of the problems that I am seeing in the prospective, because we handle all of our cases the same way, once we get the block, are the pre block preparation.

COFFEY, Q.C.:

Q. Now, doctor, in respect of the prospect of and current cases, okay, the current process and I'll refer to them, you've classed them as the prospective cases, you have been reporting them?

DR. MULLEN:

A. Oh, yes.

COFFEY, Q.C.:

Q. From Newfoundland and Labrador. How confident are you in relation to the accuracy of your reporting of ER and PR in respect of those cases?

DR. MULLEN:

A. I am as confident as the cases that I do in-house that are properly prepared because we work extremely---"we" meaning the technologists work extremely hard to get me a

Page 165

slide that's interpretable. And there are very rare cases that I will say "Uninterpretable. Please send another block." But the material we have is, before I diagnosis it, because again, remember, I discussed the philosophical, there is nothing you can do about the retro, but going forward, if I'm unsatisfied with the amount of material or the quality of the material, I'll ask for another block and then repeat it or we will work very diligently to get multiple sections to get interpretable material.

COFFEY, Q.C.:

Q. And that's for the current -

DR. MULLEN:

A. Yeah, that's current.

COFFEY, Q.C.:

Q. - prospective cases. From this province?

DR. MULLEN:

A. Yes.

COMMISSIONER:

Q. Sorry, Mr. Coffey, I'm just going to jump in here again. I'm just thinking in terms of organization of your lab, I'm just thinking in terms of lab organization.

Page 166

DR. MULLEN:

A. Yes, um-hm.

COMMISSIONER:

Q. So then the business of proper fixation and processing is critical to the validity of your test but also it's not done properly, someone else down the line in your position, a pathologist, will have to either go back to the technicians and get further work done or perhaps if the lab is being properly run, the technicians themselves will recognize a problem and deal with it?

DR. MULLEN:

A. That's correct.

COMMISSIONER:

Q. But it seems to me that that means the cost per test of your operation would be much higher if your fixation, etcetera, were not done properly in the first place because the technicians and the pathologists have to take more time to get what they need to read the test. Is that -

DR. MULLEN:

A. In general, yes, yes. If your criteria--if your criteria for signing out are sufficiently

Page 167

high, you will send the material back to be repeated.

COMMISSIONER:

Q. Okay.

DR. MULLEN:

A. If you set your criteria low, that you'll accept anything, then it wouldn't make much difference. It would take longer for the technician to make a bad slide because they try to work at it, but if you're sending back for perfection, yes, it would take much longer and the cost would go up.

COMMISSIONER:

Q. Okay. Thank you.

COFFEY, Q.C.:

Q. Doctor, in respect of the retrospective cases, retrospective studies that you did.

DR. MULLEN:

A. Yes. So that -

COFFEY, Q.C.:

Q. The '97 to 2005, not the slide review but the retrospective study which the results of which you reported in a spreadsheet format?

DR. MULLEN:

A. Yes.

Page 168

COFFEY, Q.C.:

Q. Okay. You've described for the Commissioner, you know, the artifacts and problematic aspects of what you were seeing?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Okay. But in terms of the actual reporting itself, when you reported something as from your perspective positive in the sense of an ER and/or a PR result greater than one, okay, and in your world that's a positive?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. If you reported it as positive, how confident are you in respect of the validity of that report? If you called it as a positive, are you satisfied that it was a positive aspect to the tumor cells?

DR. MULLEN:

A. Yes. Yes, I was confident that I would not report a positive unless I could justify in my own mind that it was positive. I think what I would like to clarify is some of the e-mail

Page 169

discussion we had, or discussions yesterday when we were--Dr. Cook and I were going back and forth as to whether something was, I think the one or two cases where I talked about the outside versus--so the percentage increased because the tissue is better fixed, but in those cases we were quibbling over, I shouldn't say quibbling, that minimizes the extent of the conversation. We were discussing the issue of basically what a positive is. In my world a positive is greater than one, it's low positive but it's positive. In his world I believe it's, after discussion with you, it's ten. So as far as I was concerned, it was positive, the patient was, in my world, the patient would be eligible for therapy. So whether I say it's a five or say it's a 12, it's not--it is a positive.

COFFEY, Q.C.:

Q. And in terms then of the--from your own perspective, you know, as a professional, when you reported in the retrospective spreadsheets that you called somebody an ER greater than one, whether it was two all the way up to 100,

Page 170

or a PR all the way from greater than one, two, up to 100, and that you were satisfied that a physician could -

DR. MULLEN:

A. Could act on that.

COFFEY, Q.C.:

Q. - could act upon that information.

DR. MULLEN:

A. The only reason we put it in a--well, I shouldn't say the only reason, one reason we put it in a spreadsheet was to facilitate reporting, and the other, I'm not sure of the legalities in Newfoundland, but in Ontario, the Public Hospital Act, if I issue a report, it has to become part of the patient's chart. So it was not my responsibility, or I shouldn't say not the responsibility, it's not my--it's not--I wished to have something put on the patient's chart until it had been reviewed by the Newfoundland pathology department. I mean, I was issuing reports and it was my understanding that they would look at my slides before they did anything, just to double check. I mean, out of a--there may have been a few maybe that they would

Page 171

interpret differently, which is legitimate, as I remember if I recall the discussion on the invasive carcinoma issue with Dr. Denic that I referred to yesterday, the three blocks from Western Memorial, two DCIS, one invasive, and I mean, pathology is not black and white. It's--as we've shown, it's various shades of brown, and pink and blue, and within and between sort of departments and pathologists, there are legitimate disagreements. I'm not saying they're misdiagnoses. They could be variant in interpretations and they are legitimate and no one, in my profession, takes exception to being asked to review something. It's not a personal slight. It's we are there to provide the correct diagnosis if somebody else has reviewed it and they don't agree or they want to question or they want further, it is entirely legitimate and we're happy to do it.

COFFEY, Q.C.:

Q. Doctor, the antibodies used for ER and PR -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Page 172

Q. I gather Mount Sinai uses two particular antibodies -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. - one for ER and one for PR, and Ms. Wegrynowski and, I believe, Dr. O'Malley have referred to them, as have you. For example, for ER, are there other antibodies that can possibly be used?

DR. MULLEN:

A. Yes, there are multiple antibodies. Various companies, various clones within that can be used for both ER/PR. Did Dr. O'Malley and Dr. or Ms. Wegrynowski comment on why we use those specifics?

COFFEY, Q.C.:

Q. If they did, it won't hurt for you to remind us.

DR. MULLEN:

A. Okay.

THE COMMISSIONER:

Q. Work on that old preacher's principle. Tell me three times and I might -

DR. MULLEN:

Page 173

A. I'm going to tell you what I'm going to tell you. I tell you what I tell you and then I told you what I told you. Okay. Good, that's what I teach my students. It also shortens the lectures. Just very quickly, Dr. O'Malley was involved in the study that basically established the one percent guideline, the basis of that, and she believes, and she's the lead in the ER/PR and HER2 area, that she believes that based on her literature review and personal experience that the best validated antibodies and the best cut-off points with clinical validation are by Allred, so he may not be the final author on the papers, but the two ER and the PR papers and I have the references if we need them. So anything greater than one percent for ER, I think she may have gone through. It was using an Allred score. There's the percentage and the intensity, so a score greater than three.

MR. BROWNE:

Q. Commissioner, excuse me, if the witness can be shown P-1728, page six, that's Dr. O'Malley's presentation and he may be able to tie it together.

Page 174

THE COMMISSIONER:

Q. All right, sure.

MR. BROWNE:

Q. Yes, there's the reference to -

DR. MULLEN:

A. Okay.

THE COMMISSIONER:

Q. The Allred score, yes.

MR. BROWNE:

Q. Allred score.

DR. MULLEN:

A. Yes, all right.

THE COMMISSIONER:

Q. Thank you, Mr. Browne.

DR. MULLEN:

A. Don't like my locking it down.

MR. BROWNE:

Q. That would be page six.

THE COMMISSIONER:

Q. Page?

MR. BROWNE:

Q. (Inaudible).

THE COMMISSIONER:

Q. What page number are you talking about?

MR. BROWNE:

Page 175

Q. (Inaudible).

THE COMMISSIONER:

Q. I do recall -

DR. MULLEN:

A. Do you want me to whip through and I can pick it up?

THE COMMISSIONER:

Q. Of course, easy.

DR. MULLEN:

A. Here we are. This would be the--sorry, do you have this? So the one in the lower left-hand corner, or the one on the left, so the Allred score was a combination of proportion or the percentage. So zero would be none. One would be less than 100, less than one percent. Two would be one to ten percent. Ten percent to 33 percent, 33 percent to 66 percent, and then over 66 percent would be the score, and then the intensity would be zero--I think I alluded to this yesterday. Zero would be negative. One is weak. Two is intermediate and three is strong, intermediate or moderate. So the original score was anything greater than three. So that would be--sorry, anything greater than two, so three and above. So as

Page 176

few as one percent of cells that were weakly positive would respond to therapy, both chemotherapy--sorry, would respond to Tamoxifen, would respond to hormone manipulation, and for both the ER and PR, use in the term in one of the papers, they dichotomize the patients into two groups, those who responded and those who did not respond. So anybody less than one percent did not respond. There was a significant different rather in the response between less than one percent and one percent and greater. Now I'm not saying that somebody who--or the paper doesn't say that somebody who is two percent will respond to the same extent that somebody who is 95 percent, but there is a significant different in response at P less than--I think it was P less than .0014, if you do the manipulation, it's P less than .01, if you do the--take out the multiple variables. But at least a statistical significant difference in response, rate of response to hormone manipulation for both ER and PR greater than one percent. So that's why we use the one percent.

Page 177

COFFEY, Q.C.:
Q. That's your one percent. Doctor, in terms of the various types of antibodies, okay, why does Mount Sinai use the ones it does?
DR. MULLEN:
A. Because, as I was mentioning, Dr. O'Malley, when we established these, these are the best clinical and technically--best, the best validated bodies, both--validated antibodies, both clinically and technically.
COFFEY, Q.C.:
Q. Okay, clinically and technically?
DR. MULLEN:
A. Yes, so this criteria for scoring, plus--so that would--plus how they were--we followed the guidelines for staining.
COFFEY, Q.C.:
Q. I take it though, Doctor, as there are other antibodies, I take it, that are perceived to be acceptable by at least certain groups of pathologists?
DR. MULLEN:
A. Yes, there are. That doesn't preclude other hospitals from using other criteria, other antibodies. I mean, this is what we've

Page 178

established, based on the literature, her reading of the literature, and our clinicians accept this practice.
COFFEY, Q.C.:
Q. Doctor, if St. John's was, for example, back between 1997 and 2005, was using a different antibody than Mount Sinai was, if it was, during any of that, all or any of that period, for ER or PR, would that have made any difference to what we've talked about here, in terms of your review, do you think?
DR. MULLEN:
A. It wouldn't have made a difference in the sense of the reactivity. It might have made a difference, depending on how those antibodies had been validated clinically, whether one percent or ten percent or 30 percent was the valid cut off.
COFFEY, Q.C.:
Q. Okay.
DR. MULLEN:
A. It would be not the technical, but the clinical -
COFFEY, Q.C.:
Q. Clinical end of that?

Page 179

DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. And you say you'd have to go talk to the oncologist?
DR. MULLEN:
A. Yes, the oncologist.
COFFEY, Q.C.:
Q. And/or the pathologist who picked those particular antibodies?
DR. MULLEN:
A. Yes. You have to be very careful. I'm a pathologist, not a oncologist. So basically, this is--I'm giving you the party line from the pathology side. It's up to the Commission to--they can totally ignore my reports, which they do quite frequently. They have their own ideas. Not so much on this, but on other things I do.
COFFEY, Q.C.:
Q. Doctor, with respect to this, I noticed in the reports that we've looked at, the actual reports where you--the consults, or the samples we looked at.
DR. MULLEN:

Page 180

A. Yes, prospective, yes.
COFFEY, Q.C.:
Q. You do note the actual antibodies used?
DR. MULLEN:
A. Yes, that's a -
COFFEY, Q.C.:
Q. And why is that?
DR. MULLEN:
A. The College of American Pathologists, the requirement that we give the antibody and the procedure. If I remember yesterday, we mentioned it was 6--for estrogen receptor it's 6F11 LSAB, which is linked strepped avidin procedure. There are other polymer procedures, horseradish peroxidase procedures, but that's the one we use for this one, and PGR1294 for progesterone.
COFFEY, Q.C.:
Q. Okay, and the purpose in you so reporting that is what? Because it's required?
DR. MULLEN:
A. Because it's a requirement for our accreditation, plus I don't think it would make any difference to the clinicians, as they never even sort of--I don't think they read

Page 181

that line. They look at the number and then they look at our interpretation.

COFFEY, Q.C.:

Q. But someone, I take it, afterward going back -

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Looking at it, would be able to say, okay, three years ago or five years ago, Dr. Mullen reported these percentages, but he was utilizing these particular antibodies and this particular method?

DR. MULLEN:

A. Yes, yes.

COFFEY, Q.C.:

Q. Bearing that in mind, these are the numbers he got, okay.

DR. MULLEN:

A. And also, if you look at the recent reports, we reference everything.

THE COMMISSIONER:

Q. I'm sorry, you?

DR. MULLEN:

A. We reference what thresholds we use.

THE COMMISSIONER:

Page 182

Q. Okay.

DR. MULLEN:

A. We give the threshold and we have a reference to the threshold.

THE COMMISSIONER:

Q. Yes.

DR. MULLEN:

A. Motion is the one paper and the other.

COFFEY, Q.C.:

Q. Doctor, could you tell the Commissioner, please, what, within Mount Sinai itself, in respect of, for example, IHC staining, in particular, ER and PR, what sorts of quality assurance measures are you, as a pathologist, involved in or are you aware of?

DR. MULLEN:

A. We have two, quality assurance and quality control. The quality assurance, we have four programs that we belong to. One is--let me just QMPILS, which is the Quality Management Program in Laboratory Services, which is from Ontario. There is the UK NEQAS, which is United Kingdom National External Quality Assurance Service. There is the College of American Pathologists, which is--and also,

Page 183

there's a new initiative in Canada through the College of--Canadian Association of Pathologists called CIQA, which is--I'm sorry, Immunohistochemistry Quality Assurance that has just started, which is looking at ER/PR and HER2 and if you read the Globe and Mail in the beginning of June, there was a large front page article on that, and those are the four that we--the external quality assurance, and then we have internal quality control in the laboratory and within the Department, Dr. O'Malley and I, since we are the major readers, have reviews. She'll look at mine, I'll look at hers, and she also--because she presents at tumor boards, which are review of all the cases, she'll review all of the--these are the in-hospital cases and compare. Now when we talk--and also, with all of these external, she and I will read separately and compare and contrast our results. Well, we should--we use the term "blinded". It's not a good term for pathologists. But I will interpret without knowledge of her results. She will interpret without knowledge of my results, and then "boomp, boomp, boomp", and

Page 184

then, you know, if she says 10 and I say 12, like minor. But if she says 100 and I say zero, then we have a discordance.

COFFEY, Q.C.:

Q. Or for example, if you said 10 and she says 70, I take it that would be -

DR. MULLEN:

A. That'd be fine. Fine, I mean, we -

COFFEY, Q.C.:

Q. No, I'm sorry, 10 and 70.

DR. MULLEN:

A. Oh, sorry. No, that would be a major issue, major issue. Major issue, major, major, major.

COFFEY, Q.C.:

Q. And in terms -

DR. MULLEN:

A. But we had -

COFFEY, Q.C.:

Q. What would that--if that was to happen, I take it you'd both make inquiries then as to what had happened?

DR. MULLEN:

A. Yes. "Can't you see?" that sort of thing, yes.

Page 185

COFFEY, Q.C.:
Q. Okay.
DR. MULLEN:
A. We would sit down and--we'd sit down and resolve the issues. I mean, it's not so much for the ER--ER and PR in our lab is robust, well established and we're quite happy with it, and it's--although it's sensitive to fixation and all the other things, within our laboratory, we've sort of accommodated for those things, especially for the in-house cases. The one we're having great difficulty with are the HER2's because they're very sensitive to proper fixation processing, etcetera, etcetera, etcetera, and it also has tremendous cost implications because if you have to move from the standard immunohistochemistry to resolve either discordant results or equivocal results, then it has a cost implication and a time implication, because you have to do what we mentioned yesterday as fluorescence in situ hybridization. So those are--and we are--we do, last year we did 1866 of those. I had to do that for a quality management program.

Page 186

They wanted to know how many we reported. Those have--we have no control over the fixation. We have--there are guidelines which I mentioned earlier, the ASCO, College of American Pathology guidelines that tell fixation, etcetera, etcetera, and how to do, but we really have no control over it.
COFFEY, Q.C.:
Q. When you say control over it, I take it within Mount Sinai you would have control over -
DR. MULLEN:
A. Within, we have control, but it's the material coming from other institutions. I mean, there are very rigorous criteria for how to submit and how to analyze, but at the end of the day, what people decide to send to us, we can't deal much with.
COFFEY, Q.C.:
Q. Doctor, in terms of then, the idea that you would look at occasionally review in a blind, blinded way, Dr. -
DR. MULLEN:
A. (Unintelligible).
COFFEY, Q.C.:
Q. - something Dr. O'Malley had already looked at

Page 187

and vice versa. Does that occur for everything or does it occur on a percentage base, like so many every so many cases, or -
DR. MULLEN:
A. Which, the reviews?
COFFEY, Q.C.:
Q. The reviews, that sort of review.
DR. MULLEN:
A. It's 100 percent of the internals. She would review mine or whomever was presenting at tumor boards would review my cases and her cases, if she were not presenting, and that's 100 percent. The ER/PR is not as rigorous. It's basically because HER2 is not reported the same time. She will have done the initial review and then I will do the HER2 and since I'm putting my name on the final report and vice versa, she's putting her name on my final report, I want to make sure that I agree with that result. So that's--that would be sort of we're on, we alternate. So it would be a small, but not insignificant number of cases.
COFFEY, Q.C.:
Q. And Commissioner, I'm going to ask we take break now for lunch. I'll come back, I have

Page 188

just a couple of other questions, but it may take the doctor some minutes to actually answer them.
THE COMMISSIONER:
Q. All right.
COFFEY, Q.C.:
Q. And then continue on with the other lawyers.
THE COMMISSIONER:
Q. All right then. We'll take the luncheon break, five after two.
COFFEY, Q.C.:
Q. Thank you, Commissioner.
(LUNCH BREAK)
THE COMMISSIONER:
Q. Please be seated. Mr. Coffey.
COFFEY, Q.C.:
Q. Thank you, Commissioner. Dr. Mullen, in relation to the matter of the breast tissue of--breast tissue samples that you're seeing from Newfoundland on the prospective or current cases, you indicated that it's your view that they have--it has gotten better over time, but it still has a ways to go?
DR. MULLEN:
A. There are occasional cases that I'm not

Page 189

satisfied with the processing fixation issue, but overall, there's been a marked improvement over time.

COFFEY, Q.C.:

Q. And with respect to the cases, you know, individual particular blocks that you do have a concern about, how do you handle that?

DR. MULLEN:

A. Basically, two points, if I'm totally unsatisfied, don't feel I can render an accurate diagnosis, the tissue is un interpretable or obviously if there's no tumor in the tissue, I'll ask for a second block. Otherwise, as I mentioned this morning, we will repeat our--if I don't feel comfortable on the original, we will repeat our staining, both the ER, PR and if we're doing the HER2 obviously, and then if I'm satisfied that the second go is better, then I'll report it. Otherwise, I'll ask for a second block.

COFFEY, Q.C.:

Q. And Doctor, I take it overall then though, in respect of any one patient, I take it when you finally do issue a report in respect of ER and PR, HER2/neu, from your perspective, are you

Page 190

satisfied that you can do so?

DR. MULLEN:

A. Yes. When I put my name to the bottom of the report, I put my professional integrity on the line that it's correct. The technical work and the professional interpretation are correct and that the clinician can act on the results.

COFFEY, Q.C.:

Q. Doctor, you did also refer, before the lunch break, to the idea that matters involving fixation or processing of--and processing of tissue, and/or processing of tissue, that might affect breast tissue and ER/PR results and possibly HER2/neu results as well, any inadequacies in the fixation process for the processing of tissue process that might affect breast tissue, might also affect other tissue?

DR. MULLEN:

A. That's correct.

COFFEY, Q.C.:

Q. Is there anything about breast tissue and ER/PR and HER2/neu tests that make breast tissue particularly susceptible though to problems as a result of fixation or processing

Page 191

inadequacies?

DR. MULLEN:

A. Well, if you recall the slide show from this morning, or my peach analogy, breast specimens tend to--well, breast specimens, there are three types to surgical pathology. One is a core biopsy, essentially where a needle is placed in the breast and a small core, maybe one or two millimetres in diameter, three or four millimetres or maybe a centimetre or two in length, is extracted. That's put in formalin and then sent to the laboratory. There's immediate fixation and if they're using the proper amount of--or using the proper fixative, the ten percent neutral buffer formalin, I would not expect there to be an issue with the fixation. So that type of specimen is covered.

The next type of specimen, and I'll put the two together, one is called a lumpectomy where a small amount of breast, the tumor and a rim of non-tumorous breast is removed, and a mastectomy where skin and breast are removed. Those require more extensive handling immediately. That's where I have the concern

Page 192

from where the specimen is removed from the OR that it be put in formalin, be placed in a refrigerator, if it's not immediately transported to the laboratory, and then serially sliced so that the fixative is through the slice and then whipped with the--we use paper towel, other materials can be used. Immediately fixed, so that the inherent deterioration that occurs in a specimen, a natural process, is inhibited as quickly as possible, so that we have preservation of the nuclear detail, the proteins, and essentially the antigens that the antibodies react to.

COFFEY, Q.C.:

Q. Doctor, and are there--in terms of the full--well, I gather the full spectrum of possible pathology tests, both special stain tests and IHC tests and so on, are there any particular tests that are prone to being more affected by inadequacies in fixation and processing than others?

DR. MULLEN:

A. Yes, there are three categories of stains, three categories, yes. There's routine H & E and then there are called the histochemical

Page 193

stains, where we'll stain for organisms or products within the cell, such as we do--I won't enumerate the types of stains, but anyways, stains for fungi, stains for micro bacteria. Those are fairly rigorous and you can do them on less than optimal tissue, but anything that requires preservation of an antigen, so with immunohistochemistry, we're trying to detect substances that are present on the outside of the cell, on the cell membrane, substances that are present in the cytoplasm, so the border between the cell and the nucleus and within the nucleus.

So if you think of a cell, we'll go to another one of my food analogies, if you think of the cell as a fried egg. So we are trying to detect--if we're trying to do membrane, we're trying to detect the outskirts or the outside of the white. If we're trying to detect the cytoplasm, we're detecting the white. If we're doing the nucleus, we're trying to detect the yolk. Now think of a fried egg. Formalin basically is cross links proteins. It's the same as heat, heat for the egg, the same effect. So if you have

Page 194

something that's not fixed, so if you have your yolk that's not fixed -

COFFEY, Q.C.:

Q. Or optimally fixed, I take it.

DR. MULLEN:

A. Beg your pardon?

COFFEY, Q.C.:

Q. Fixed or at least, or optimally fixed, are you talking -

DR. MULLEN:

A. Not optimally fixed. So basically, if you take the egg out, the yolk runs. So you have nothing left. That's the analogy of the hollowed nucleus. So you want--those of you who like sort of hard eggs, but anyways, that's the optimum. You want a well fixed cytoplasm, so the white doesn't run and you want the yolk fixed and yellow so it doesn't run. So if it's the equivalent in a cell that it's not fixed, the yolk would flow out basically. So that's the analogy. Pathology uses a lot of food analogies.

COFFEY, Q.C.:

Q. And Doctor, in respect of that then, I take it these particular immunohistochemical stains

Page 195

and antibodies, I take it, they require, all things considered, a more careful attention to rigorous fixation or processing protocols?

DR. MULLEN:

A. Yes. The handling should--the handling has to be extremely rigorous, if you want to compare one to the other.

COFFEY, Q.C.:

Q. And Doctor, in respect to this entire matter, because you've been involved in the retrospective study, our analysis, you were involved in what I will refer to as the slide review in 1998 (sic.), and Doctor, from your perspective, the pathologists who originally reported these cases back in '97, '98, '99, 2000 all the way up through 2005, in your view, should it have been apparent to them, one or more of them, that there was a problem?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. And why is that?

DR. MULLEN:

A. The quality of the material was so inadequate that the interpretation, both of the H & E

Page 196

sections in some cases, as well as the interpretation--not just the interpretation, but the actual material that was present on the ER and PR specimens was less than certainly optimal and in some cases, almost less than would be required for analysis.

COFFEY, Q.C.:

Q. As an example, Doctor, there were two, I, in fact picked in particular when we were dealing with the discordant label that you'd put on, and I had referred then to 1998 slide review. It's actually 2008 slide review. That's my--misspoke then. You looked at the slides in 2008. Doctor, where, for example, there was no internal control present on the original slide, original ER slide or original PR slide as created in Newfoundland, when a pathologist looked at that, would he or she, in your view, throughout the period '98, '97 through 2005, should he or she have noticed that there was no internal control tissue present?

DR. MULLEN:

A. Yes, oh yes. That would be one of the basics for assessment.

COFFEY, Q.C.:

Page 197

Q. And if there was internal control tissue present, but it, at least in your view, had not stained, based upon the slide review, should that have caused him or her any concern?

DR. MULLEN:

A. It would cause concern. It would cause, not--maybe concern is too strong. It would cause pause, because as I have mentioned, it's not an all or none phenomenon. 90 percent in the post-menopausal patients with cancer versus 80 percent in the pre-menopausal. But a caution, not a stop.

COFFEY, Q.C.:

Q. And in terms of, for example, you've referred to exploding areas of the slides.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Should that have caused, in your view, pathologists who saw--any other pathologist who saw that concern, at least to at least make further inquiries?

DR. MULLEN:

A. Yes, I think yesterday I indicated that one

Page 198

maybe, two umph, and three, I'm not going to repeat the phrase, but three, major concern. Major, major, major concern.

COFFEY, Q.C.:

Q. And the phenomenon of the hollow nucleus, nuclei, I'm sorry, same thing, I take it?

DR. MULLEN:

A. Same thing, and to extend to the necrosis, yes. All of those, I mean, in any one case, one of those would be worrisome, but to have all of those in the same case or to have a sequence of these over a short period of time or even a long, extended to a longer period of time would cause great concern.

COFFEY, Q.C.:

Q. Doctor, we have seen here, if we could bring up Exhibit, please, P-1767? This is an article entitled "Recommendations for Improved Standardization of Immunohistochemistry." It's one, prepared by certain individuals and members of the ad-hoc committee on immunohistochemistry standardization. It was published in June of 2007. Dr. Pritzker has been referred to it, but I gather, Doctor, from what we have heard so far that these are

Page 199

recommendations by a group of pathologists setting out, from their perspective, recommendations for improved standardization of immunohistochemistry and they talk about here particular aspects of immunohistochemistry that can be problematic at times if not properly attended to.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. I understand, Doctor, that you thought it might be helpful to go through at least some of this with the Commissioner, in terms of pointing out certain things.

DR. MULLEN:

A. Rather than taking you through the entire article, I thought the abstract.

COFFEY, Q.C.:

Q. Abstract, yes.

DR. MULLEN:

A. Those of you familiar with medical literature, I'm not sure what the legal--not familiar with legal literature, but medical literature, the abstract is basically quick synopsis and usually covers the points that are then in the

Page 200

article in greater detail.

COFFEY, Q.C.:

Q. Doctor, in our world, that's a headnote.

DR. MULLEN:

A. A which?

COFFEY, Q.C.:

Q. In our, the legal world, we call it a headnote.

DR. MULLEN:

A. Oh, headnote, okay. So I would--in this document, I would take your attention to the sentence that contributing factors. So -

COFFEY, Q.C.:

Q. That's about five or six lines down.

DR. MULLEN:

A. Yes, the third sentence.

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. Now "the contributing factors were established"--this is what they, the ad-hoc committee felt to be major causative factors for the lack of reproducibility, consistency and if you go--if we go through it, "contributing factors were established to be

Page 201

under fixation and irregular fixation." This we've been harping on, both yourself and myself, for the last two days. "Use of non-formalin fixatives and ancillary fixation procedures divested from a deep and full understanding of the IHC assay parameters." That is not relevant in the--well, I shouldn't say it's not relevant. If they were using--if they being the--if the contributing laboratories were not using formalin fixatives, neutral ten percent buffered formalin, if they were making their own or they were storing it improperly or they weren't testing the pH, that could be an issue. But if they're buying the standard pre-made ten percent neutral buffer formalin, storing it properly, testing the pH on each package, then that would not be an issue. But then again, for size, the fixation would have--the specimen would have to be cut and wick'd, and if the laboratory did not have a deep and full understanding of the IHC assay parameters, then they would run into problems.

"Minimal or absent IHC assay optimization," there again, when we were

Page 202

discussing, I believe it was this morning, the issue with the Ventana results where we had both nucleus and cytoplasm, that would have been an issue in this case. I'm not sure about the initial validation and optimization of the IHC assay in '97 and continuing through. I don't have any documentation on that and I really can't comment on it. And "lack of a standard system of interpretation and reporting," we saw in the review that I did of--that I reported in April of the cases from--that were selected and sent to me in March that we had reports that were negative, completely negative, moderately positive, rare, that sort of thing, and then some that gave a qualitative--sorry, quant--both qualitative and quantitative. So, and there was no documentation, not that I would expect necessarily documentation of their pattern of interpretation, but the reporting should be standardized.

So then, the article, it goes through suggestions, but there's nothing here that either Trish on Tuesday or Wednesday, or myself and even Dr. O'Malley and Dr. Pritzker,

Page 203

there's nothing here that is new or not in practice in the majority of laboratories that I'm aware of.

COFFEY, Q.C.:

Q. Doctor, in terms of the retrospective study, there's one thing I wanted to ask you about, retrospective review that you conducted, there was, I take it, a particular format that you followed for--format in the sense of procedure followed, in terms of the controls being checked and so on over time. Did that ever change? Did the approach you took ever change?

DR. MULLEN:

A. Oh, yes. I don't have the exact date, but I--we get--we meaning the Mount Sinai, if you recall the e-mails, getting a lot of pressure to speed things up, and we made a decision, in conjunction with Eastern Health, we asked their agreement to this, that we would stop doing the negative controls with each specimen. The reason we did that was to increase the capacity on the machines to increase the throughput. We felt that we had established the negative control on, I

Page 204

believe, the first it may have been 200 or so cases, and we didn't--and we believed that it had no material impact to the results, and we had Eastern Health's concurrence or agreement to actually doing that. In retrospect, probably shouldn't have, but we should have stuck to our guns and gone through slowly, but it was an issue to get the results out as quickly as possible, and I don't--sorry.

COFFEY, Q.C.:

Q. These are external negative controls?

DR. MULLEN:

A. No, not the--yeah, external negative controls, not within a--had nothing to do with a specimen.

COFFEY, Q.C.:

Q. And they aren't the external positive controls?

DR. MULLEN:

A. No, the external positives were always run. Our policy in each case is to do a positive external control for each immunostain we do and a negative control with each specimen that we do. So we'd have one ER, one PR and one negative control. It's basically to eliminate

Page 205

the possibility of non-specific staining. Now, in my defence, we had established the protocol. There was no deviation from case to case. All of the reagents were the same. All of the procedures were the same, push the button and away it goes. So it was a calculated risk and as I said, we felt that it had no material impact on the results.

COFFEY, Q.C.:

Q. And when you say "no material impact" in this context, I take it that -

DR. MULLEN:

A. Would be -

COFFEY, Q.C.:

Q. - you were professionally comfortable and prepared to give the results?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Despite the fact that for a certain period of time in respect of the retrospective cases only, I take it?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Page 206

Q. That the external negative controls were not being utilized?

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. Okay. And the purpose of such a negative external control is to eliminate or rule out the idea of non -

DR. MULLEN:

A. Non-specific binding. So basically you have-- you prepare two solutions. One has the antibody, or in this case would have the 6F11 or PTR1294, one substance, and the negative control would have everything except the antibody. And then the issue is a non-specific. When you're setting up--when you're validating, your negative control would be-- would have the class of immunoglobin but wouldn't have the specific antibodies. So there are two types of negative control, when you're validating or optimizing and validating and then when you're running.

COFFEY, Q.C.:

Q. And these related to the running, I take it?

DR. MULLEN:

Page 207

A. Yes, this related to running. All of our optimization and validation had the negative control and some of these--the majority, I shouldn't say majority, large number of these cases had the negative control, as well. So as I said, it was a through put issue.

COFFEY, Q.C.:

Q. They're the questions I have, Commissioner, thank you.

COMMISSIONER:

Q. Thank you. Mr. Pritchard.

MR. PRITCHARD:

Q. Commissioner, I don't have any questions for this witness. Thank you.

COMMISSIONER:

Q. Mr. Simmons.

DR. BRENDAN MULLEN, EXAMINATION BY MR. DANIEL SIMMONS

MR. SIMMONS:

Q. Thank you, Commissioner. Good afternoon, Dr. Mullen.

DR. MULLEN:

A. Mr. Simmons.

MR. SIMMONS:

Q. We've met before. I'm Dan Simmons, I'm the lawyer for Eastern Health. I do have a few

Page 208

questions for you. I'm going to start with something that you dealt with late this morning in your examination by Mr. Coffey. I just want to confirm some evidence that you've given. You've told us quite a bit about the retrospective review which you did which was the review of the slides produced at Mount Sinai from blocks that had been produced in Newfoundland from 1997 to 2005. You've told us of the issues that you identified concerning fixation and processing, and concerning internal controls?

DR. MULLEN:

A. Yes.

MR. SIMMONS:

Q. With those slides. But do I understand correctly that you've also told us that you were able to sign out and report a result on all those specimens, an ER and PR result for each of those specimens in the retrospective review?

DR. MULLEN:

A. That is correct.

MR. SIMMONS:

Q. Yes. And you are satisfied that you've

Page 209

reported an accurate result in accordance with the standards that you as a professional pathologist with expertise in the area apply to assessment of those tests?

DR. MULLEN:

A. Yes, that is correct.

MR. SIMMONS:

Q. Okay. So that we have every reason to be confident that the patients who had been relying on those retest results are able to rely on those?

DR. MULLEN:

A. Yes.

MR. SIMMONS:

Q. Okay. And in respect -

DR. MULLEN:

A. That, we're referring to the stained slides from Mount Sinai?

MR. SIMMONS:

Q. Yes.

DR. MULLEN:

A. Yes. So -

MR. SIMMONS:

Q. Exactly.

DR. MULLEN:

Page 210

A. - the material that we actually stained, yes.

MR. SIMMONS:

Q. Yes, correct.

DR. MULLEN:

A. Yes.

MR. SIMMONS:

Q. And the other cases, the group, large group of cases you've spoke about are the what you've called the prospective cases which are the, I'll think of them as the new -

DR. MULLEN:

A. The go forward, yes.

MR. SIMMONS:

Q. The new cases, the go forward ones that you began to look at from August of 2005 and for three of the health authorities in Newfoundland you continue to review--have continued to review up until recently?

DR. MULLEN:

A. Yes. Yes, that's right. Central, Labrador, Grenfell and Western.

MR. SIMMONS:

Q. And Western?

DR. MULLEN:

A. Yes.

Page 211

MR. SIMMONS:

Q. Right. And the same questions for those, we have no reason to, in any way, doubt any -

DR. MULLEN:

A. No.

MR. SIMMONS:

Q. - of those results that you've reported back from Mount Sinai?

DR. MULLEN:

A. No. I use the same standards that I would report to any other.

MR. SIMMONS:

Q. Right. So even though you've told us that at the beginning of this process in August '05 you were seeing some issues with fixation and processing and you still see some occasional issues with it today, that should not cause us to doubt the reliability of those test reports in any way?

DR. MULLEN:

A. No.

MR. SIMMONS:

Q. Good. Okay. Eastern Health started retesting its own samples in about February, March of 2007?

Page 212

DR. MULLEN:

A. Yes.

MR. SIMMONS:

Q. So if I understand correctly, up until probably last week between that time, February, March of '07 and very recently the only ER/PR samples that you would have had stained at your laboratory and looked at yourself would be the quality assurance samples that were sent from Eastern Health?

DR. MULLEN:

A. From Eastern Health, yes.

MR. SIMMONS:

Q. Right. The other authorities continued to send their own samples?

DR. MULLEN:

A. Yes, that is correct.

MR. SIMMONS:

Q. Yes. And when looking at those quality assurance samples would you assess the quality of the fixation and processing -

DR. MULLEN:

A. Yes. If -

MR. SIMMONS:

Q. - as part of that process?

Page 213

DR. MULLEN:
A. If you recall the spreadsheet that I use for my standard reporting, the ER--the tumor type ER/PR, internal control, fixation, processing, it was exactly the same.
MR. SIMMONS:
Q. Right. And if there were any problems with fixation and processing of those samples, you would report them back to Eastern Health?
DR. MULLEN:
A. Yes, that is correct.
MR. SIMMONS:
Q. And have you had to report back any issues in relation to those with the QA samples?
DR. MULLEN:
A. No. No, there were 39 samples and I don't believe I've reported.
MR. SIMMONS:
Q. Okay. And we've seen through some of the documentation that it was probably around May of '07 that you would have looked at the first of those, of those samples? I think we saw a reminder e-mail from May.
DR. MULLEN:
A. Yes, April. They started it in March, so I

Page 214

would say April, yes.
MR. SIMMONS:
Q. Right, okay. So from April of '07 until present those QA samples have been reviewed from Eastern Health and there have been no problems that you have found with fixation and processing of the samples?
DR. MULLEN:
A. The 39, I received 39 specimens and I was able, yes.
MR. SIMMONS:
Q. Yes. Mount Sinai participates in the UK NEQAS proficiency testing program?
DR. MULLEN:
A. Yes, that's correct.
MR. SIMMONS:
Q. Do you see the reports that come back from UK NEQAS on those for your laboratory?
DR. MULLEN:
A. No, I haven't seen them.
MR. SIMMONS:
Q. Do you know if that program also assesses the quality of fixation and processing of the samples?
DR. MULLEN:

Page 215

A. I can't speak to the specifics. The only interaction I've had with the NEQAS for the ER/PR was doing the scoring.
MR. SIMMONS:
Q. Okay.
DR. MULLEN:
A. That would be Dr. O'Malley who would have dealt with that issue.
MR. SIMMONS:
Q. Right. I take, though, it wouldn't surprise you if that program also looked at that issue when they examine slides produced by their participating laboratories?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Okay. I had some questions for you concerning the tracking of positivity rates.
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. You've given us some evidence about some look-back work that you did on tests that you have reported on from 2005 to 2007?
DR. MULLEN:

Page 216

A. Yes. 2008, yeah, or -
MR. SIMMONS:
Q. Yes, up to current?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Up in 2008.
DR. MULLEN:
A. The beginning of June of 2008.
MR. SIMMONS:
Q. Right, yeah. But I'm curious in knowing a little bit more about the laboratory information system at Mount Sinai. I think we've heard from some other witnesses that there's been some change or upgrading to that system in about 2005 and a move to synoptic reporting?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Right. And prior to 2005 were you participating or do you know if the laboratory or your laboratory service was doing any kind of annual gathering of positivity rates for ER and PR testing?

Page 217

DR. MULLEN:
A. The laboratory I can't speak to.
MR. SIMMONS:
Q. No, okay. But yourself, you have been tracking your own, have you?
DR. MULLEN:
A. Yes, yes, because I use the same format, it's very easy for me to do that.
MR. SIMMONS:
Q. Right. And that's because you, as an individual pathologist, had chosen to put standardized language into the text of the pathology reports that you prepare?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. So you can search that text and know you can rely on finding all your positive tests and all your negative tests?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Do you know if other pathologists at your institution reporting ER/PR tests had adopted the same practice?

Page 218

DR. MULLEN:
A. No, they were not, they were putting--using--relying on the synoptic portions.
MR. SIMMONS:
Q. Okay.
DR. MULLEN:
A. For reporting.
MR. SIMMONS:
Q. Okay. Now, the synoptic portion has only been available since 2005?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. So prior to 2005 their reports would not necessarily have been searchable in the same way as yours?
DR. MULLEN:
A. No. They could be printed and searched that way, but automatic, no.
MR. SIMMONS:
Q. No. So you'd have to print them and go through them and manually identify the positives and the negatives?
DR. MULLEN:
A. Or we could--they could have prospectively

Page 219

just kept a log.
MR. SIMMONS:
Q. Okay. And do you know if anybody was doing it, taking -
DR. MULLEN:
A. I can't speak for other people.
MR. SIMMONS:
Q. Good, okay. And when you were interviewed in advance of this process, you were interviewed in December of '07?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. And you gave us the information that you talked about this morning where you had gone back and looked at your own ER/PR tests that you'd done for Mount Sinai, Niagara Region hospitals, Greater Niagara and Newfoundland from '05 forward?
DR. MULLEN:
A. I'd done the aggregate, everyone.
MR. SIMMONS:
Q. Yes.
DR. MULLEN:
A. And then because Newfoundland was a multi

Page 220

site, I looked at the Greater Niagara which is a multi site to see the comparison.
MR. SIMMONS:
Q. Right. And the comparison came out almost exactly the same, 79 -
DR. MULLEN:
A. 79.2 and 79.4, yes.
MR. SIMMONS:
Q. Right. And -
DR. MULLEN:
A. That was a prospective.
MR. SIMMONS:
Q. And at this point your view is that the literature suggests that it--the rate should be what?
DR. MULLEN:
A. Equivalent to that.
MR. SIMMONS:
Q. Equivalent to that?
DR. MULLEN:
A. Yeah.
MR. SIMMONS:
Q. So that review of the positivity rate for all samples coming from Newfoundland for 2005 forward suggests that the rate of positivity

Page 221

is pretty well exactly what the literature says it should be?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Which is a further reassurance that we can rely on the test results that have been reported, correct?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Yes. I'm going to go back now to some of the early testimony that you gave for Mr. Coffey. You told us some about how you became involved, and what you knew of the arrangements that had been made for the retrospective review that you became involved in. And is my understanding correct that the arrangements about what Mount Sinai, the services Mount Sinai was going to provide to Eastern Health were really made with others and weren't made with you?
DR. MULLEN:
A. That's correct.
MR. SIMMONS:

Page 222

Q. That's right. You didn't have any direct involvement in determining the scale or scope or number of tests that were going to have to be reviewed?
DR. MULLEN:
A. No. As I testified, I thought it was 50 to 100.
MR. SIMMONS:
Q. Right. But the information you obtained about those things came internally from others within Mount Sinai and not directly from Eastern Health?
DR. MULLEN:
A. No, no.
MR. SIMMONS:
Q. Right. And your involvement in dealing directly with Dr. Cook was very limited?
DR. MULLEN:
A. A series of e-mails, yes.
MR. SIMMONS:
Q. Series of e-mails. So you would report test results to him by e-mail, by sending your spreadsheets to you and there was a series of inquiries over time that you responded to?
DR. MULLEN:

Page 223

A. Yes.
MR. SIMMONS:
Q. Right.
DR. MULLEN:
A. That's correct.
MR. SIMMONS:
Q. And do you recall ever having any conversation with him to talk about things like the quality of the material you were seeing, any issues you were having, those sorts of things?
DR. MULLEN:
A. No. I recall two or three telephone conversations but I believe they were directed to speed.
MR. SIMMONS:
Q. Okay, so you did speak with Dr. Cook on a number of occasions on the telephone, then?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Okay. And he was inquiring about getting the work done?
DR. MULLEN:
A. Yes.
MR. SIMMONS:

Page 224

Q. You didn't take that opportunity to raise any of these issues of what you were observing with him at the time?
DR. MULLEN:
A. I'm trying to remember when the conversations were. Not at--no. It was the--the conversations on the quality were with Bev Carter in November.
MR. SIMMONS:
Q. Um-hm.
DR. MULLEN:
A. And then the e-mail in January.
MR. SIMMONS:
Q. Right. In which you suggested that some contact would be made?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Okay. But aside from that there was no--and did you regard it as your mandate to assesses these sorts of issues and provide some kind of report to Eastern Health or did you view your role as more limited than that?
DR. MULLEN:
A. For which set of cases?

Page 225

MR. SIMMONS:
Q. For the retrospective cases.
DR. MULLEN:
A. The retrospective, no, it wasn't my role to-- nothing could be done with the retrospective cases.
MR. SIMMONS:
Q. Right.
DR. MULLEN:
A. The prospective cases because I was--this was material that was being removed at the time and we could intervene.
MR. SIMMONS:
Q. Yes.
DR. MULLEN:
A. Or they could intervene, it would--it might have been useful for them to.
MR. SIMMONS:
Q. Right, right. And the one occassion we know of when you passed some information on was when Dr. Carter was in Toronto?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. The prospective cases, the go-forward cases,

Page 226

were they all reported as consultations with a regular pathology report sent to Eastern Health and the other authorities?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. And on those reports you've given us some description of the type of information that's included. Would you, in those reports, report on any issues relating to the quality of the specimen itself, the fixation and processing?
DR. MULLEN:
A. Yes, there was a specimen adequacy, some cases I would put sub-optimal or borderline for interpretation.
MR. SIMMONS:
Q. Right.
DR. MULLEN:
A. And then in the fourth line, I think it's fourth line in the--I don't have it in front of me, but the comment about the internal control, whether it was present or absent and whether it stained.
MR. SIMMONS:
Q. Right, okay. Now, I'm going to be bouncing

Page 227

around a little bit, I'm not going to be following the sequence of questions as chronologically as Mr. Coffey was able to do with you and I apologize for that in advance.
DR. MULLEN:
A. No, that's fine.
MR. SIMMONS:
Q. Again, very early in your evidence you did mention that prior to 2005 you were doing or seeing far fewer ER/PR tests than following that. And I believe you said you saw maybe 50 per year?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Prior to that. And another point I understood you to say when you were talking about the HER2/neu test that there are guidelines from College of American Pathologists and ASCO recently put in place?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. That sent expectation of the minimum number of HER2 tests that a pathologist should see to

Page 228

maintain competency. Did I understand that correctly?
DR. MULLEN:
A. I believe it's the number the laboratory should do.
MR. SIMMONS:
Q. Oh, the number the laboratory should do.
DR. MULLEN:
A. The number the laboratory should do.
MR. SIMMONS:
Q. Right. And so it's not the number of pathologists, it's the -
DR. MULLEN:
A. No pathologists, no.
MR. SIMMONS:
Q. - number laboratories should do?
DR. MULLEN:
A. Sorry.
MR. SIMMONS:
Q. Okay, I misunderstood that. Are there any similar guidelines that you're aware of in relation to ER/PR testing?
DR. MULLEN:
A. Not that I'm aware of.
MR. SIMMONS:

Page 229

Q. Okay. Do you know if there are any guidelines that suggests the number a pathologists should see to maintain sufficient competency to be reporting those tests?
DR. MULLEN:
A. No.
MR. SIMMONS:
Q. No. You've spoken a fair bit about the threshold for declaring a result positive and that the one that you use at Mount Sinai is one percent cells stained or greater?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. And we've heard some other evidence on that before. And am I correct in understanding that there are other institutions out there that don't adopt that standard and that have-- may still use the ten percent threshold?
DR. MULLEN:
A. Yes, that is correct.
MR. SIMMONS:
Q. Yeah, okay. And is the determination of that strictly a matter for the pathology service or is it something that should be done in

Page 230

consultation with the treating physicians, whether they're oncologists or surgeons or others?
DR. MULLEN:
A. It's certainly, it is the role of the pathologist to report.
MR. SIMMONS:
Q. Yes.
DR. MULLEN:
A. It's the role of the clinician to interpret the report and act on it.
MR. SIMMONS:
Q. Right.
DR. MULLEN:
A. If the clinician wants to act on a one percent--that's why we're very particular in giving the percentage as well as what we've established as our threshold based on the literature.
MR. SIMMONS:
Q. Right.
DR. MULLEN:
A. But it's up to the--the clinician receives the report, it's incumbent upon them to act on the report based on their guidelines.

Page 231

MR. SIMMONS:
Q. Right, on their assessment -
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. - of whether the treatment is merited based on the test result?
DR. MULLEN:
A. Beg your pardon?
MR. SIMMONS:
Q. On their assessment of whether the treatment is warranted, based on factors including the percentage of positivity?
DR. MULLEN:
A. Yes, that is correct.
MR. SIMMONS:
Q. So if in another institution the pathologists and the oncologists consulting with each other determined that they would regard a ten percent positivity level as the threshold for what they would consider positive, would that be something that you would regard as being an unacceptable uncommon approach?
DR. MULLEN:
A. No, not at all.

Page 232

MR. SIMMONS:
Q. Internal controls, you've told us that they will not always work, there are cases where you will have an internal control that stains negative, even though the test has been performed accurately and that the tumor has been properly stained and is interpretable.
DR. MULLEN:
A. That is correct.
MR. SIMMONS:
Q. There are some.
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. So aside from the retrospective review and dealing with the cases that were part of this study, in your normal practice when you encounter a test result where there is an internal control tissue present but it has not stained, what's the first thing that you do? What's the next thing that you do then?
DR. MULLEN:
A. I look to see if the tumor stained. If the tumor stained, I'm happy to report that.
MR. SIMMONS:

Page 233

Q. Uh-hm.
DR. MULLEN:
A. If the tumor hasn't stained and the internal control hasn't stained, if I have another block--if it's within the institution I have another block, I'll select that and I'll also repeat the original.
MR. SIMMONS:
Q. Okay. Do you ever go to the external control before repeating the test to determine whether the external control worked?
DR. MULLEN:
A. Well the external--I'm not--in our institution, I am not given any slides if the external control is negative. There is a gatekeep--I tried to explain yesterday, there is a gatekeeper function in the laboratory that if the external control and the internal control are questionable or not appropriate, then I don't see the case. If they're acceptable, the external control and the internal controls are acceptable to the technologist, then I receive the case and it's then my prerogative to either report the case or say it's unacceptable and send it back.

Page 234

MR. SIMMONS:
Q. So there are not occasions when you would, yourself, then go to look at the external control slide?
DR. MULLEN:
A. Very, very rarely.
MR. SIMMONS:
Q. Okay. You also told us that apart from any problems that might exist with fixation, processing, quality issues and so on, there can be situations where you will get different results on an ER/PR test if the tissue that's being tested comes from different blocks in the same specimen or even from different--at different points in a block that has been repeatedly sliced.
DR. MULLEN:
A. That's correct.
MR. SIMMONS:
Q. How much variation can you see in the scoring of an ER and PR test from--because of those circumstances?
DR. MULLEN:
A. If it's well fixed -
MR. SIMMONS:

Page 235

Q. Uh-hm.
DR. MULLEN:
A. - that unless there's a--there would not be a tremendous variability, maybe 20 percent from area to area.
MR. SIMMONS:
Q. Right. Okay.
DR. MULLEN:
A. And now the issue if it's not fixed, then there could be marked variability and that, I believe, we covered with Dr. Cook.
MR. SIMMONS:
Q. Sure, so even if there's no problem with the quality of the tissue, performance of the testing procedures, you could see up to 20 percent variation, depending on where the tissue has come from, from within that specimen.
DR. MULLEN:
A. Now if you recall, I referenced a paper that mentioned its bi-modal distribution to be ER/PR -
MR. SIMMONS:
Q. Yes.
DR. MULLEN:

Page 236

A. That 99 percent were 70 or above.
MR. SIMMONS:
Q. Uh-hm.
DR. MULLEN:
A. And the other--or zero, less than one, so there are very few that would be in the middle area.
MR. SIMMONS:
Q. Right.
DR. MULLEN:
A. So if you have a ninety which covers the 70, you certainly can't go to 110, but it would be that area.
MR. SIMMONS:
Q. Right, so if you're dealing with an institution where there has been an adoption of the ten percent cut off that we spoke of, it's conceivable then that this variation in testing from one block to another could produce test results that are either above or below that ten percent.
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. Without there being anything that's

Page 237

identifiably done wrong with the tests -
DR. MULLEN:
A. No, that's correct.
MR. SIMMONS:
Q. Or the interpretation of it. And in fact, I'll just look at one example in relation to that, P-1811 please?
DR. MULLEN:
A. This is your January 20th, '06 e-mail with the large spreadsheet of test results and we'll go to page three and see if I'm lucky enough to find the one I was looking for. Probably about ten up from the bottom, there's a sample, a specimen number 99327788?
DR. MULLEN:
A. Uh-hm.
MR. SIMMONS:
Q. And it's one that there's two blocks there for it, there's a block 1B and a block 1C, do you see that?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. And if you look across at your reported results, they were both cases where the

Page 238

internal control stained positively.
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. And they were both cases where the fixation and processing was adequate.
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. And one of them is reported as an ER of less than one, which would be regarded as negative?
DR. MULLEN:
A. As negative, less than one.
MR. SIMMONS:
Q. And the other one is an ER of two, which in your institution would be regarded as positive.
DR. MULLEN:
A. As positive, that's correct.
MR. SIMMONS:
Q. Okay. Perhaps a question I should have asked Ms. Wegrynowski, but you may be able to help me, do you know what method your laboratories use for antigen retrieval for ER and PR tests, because I understand there's different ones

Page 239

available?
DR. MULLEN:
A. Yes, we use the trishydrochloride microwave.
MR. SIMMONS:
Q. Trishydrochloride?
DR. MULLEN:
A. Microwave.
MR. SIMMONS:
Q. And do you know how long that particular method has been in use?
DR. MULLEN:
A. That is a question for Ms. Wegrynowski.
MR. SIMMONS:
Q. Okay, you don't know if it's changed over time since you've been involved?
DR. MULLEN:
A. No. It certainly hasn't changed since she's been there.
MR. SIMMONS:
Q. Exhibit P-1837 please? Doctor Mullen, this is the spreadsheet that accompanied your report on the review of the original slides that were produced from 1997 to 2005 over an eight-year period, and you've reported the results of your observations on a case-by-case basis, but

Page 240

I gather you have not done any more sophisticated statistical analysis to recognize any trends over time or anything like that from this data?
DR. MULLEN:
A. No, I have not.
MR. SIMMONS:
Q. And I had just some questions to make sure I understand the portion of this table where you stated whether the results were discordant with the Mount Sinai retest results or not?
DR. MULLEN:
A. That is correct.
MR. SIMMONS:
Q. And you've explained, I think, fairly clearly to us that you didn't have the time available to go back and cross reference each of these specimens with the table that has the Mount Sinai retest results for those same specimens.
DR. MULLEN:
A. That is correct.
MR. SIMMONS:
Q. So you couldn't do a complete comparison?
DR. MULLEN:
A. No.

Page 241

MR. SIMMONS:
Q. Between the two.
DR. MULLEN:
A. No.
MR. SIMMONS:
Q. This is just happens to be where you happen to have some information in the pathology report, you plugged it in?
DR. MULLEN:
A. Yes, that is correct.
MR. SIMMONS:
Q. So I take it from that then that we can't really use this particular table to draw any conclusions about the extent of the concordance or discordance overall?
DR. MULLEN:
A. No, it was not intended for that.
MR. SIMMONS:
Q. Right. And if we look even at the very first specimen there, the one's that ID No. 6 that you were referred to on this issue, this one here had a Mount Sinai review number of zero, for ER, which was your review of the original slide?
DR. MULLEN:

Page 242

A. That is correct.
MR. SIMMONS:
Q. And we don't have on this table what the retest result was for the new slide prepared by Mount Sinai.
DR. MULLEN:
A. No.
MR. SIMMONS:
Q. And what we have on the NL original here is that you were able to gather from the original pathology report that it was reported as negative in 1997?
DR. MULLEN:
A. That is correct.
MR. SIMMONS:
Q. And we've heard, and I expect we will hear more, that in 1997, anything below 30 percent would have been reported as negative?
DR. MULLEN:
A. Yes, but there was no--in the report I had, there was no mention of what the negative cut off was, so I really -
MR. SIMMONS:
Q. Right.
DR. MULLEN:

Page 243

A. - all I could do was put what the value was.
MR. SIMMONS:
Q. And we can look up this one and see what it is, but for the purposes of this particular report here, if you had a pathology report on this specimen that told you that Mount Sinai had retested it and it was 10 percent -
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. You would have regarded that as discordant from an original report of negative?
DR. MULLEN:
A. I'm trying to remember. I can't--most likely, I'll just leave it at that.
MR. SIMMONS:
Q. Yes, right. The categorization here in the column "Fixation and Processing" where you've indicated either adequate or poor, do I understand correctly that in reviewing these slides, while you can identify if the end result of the whole fixation and processing sequence is adequate or not, you can't differentiate by looking at the slide as to whether the problem originated at the fixation

Page 244

stage or whether it was the processing stage to prepare the block?
DR. MULLEN:
A. You might be able to suggest that it was fixation if you have nuclear detail and you have nothing on the slide or it's falling off, but if you don't have nuclear detail, that would suggest that it was a fixation issue, but to -
MR. SIMMONS:
Q. In your review, though, you have not differentiated between the two?
DR. MULLEN:
A. No.
MR. SIMMONS:
Q. So the most we can say if you've got poor, the most we can say is that somewhere in that process from the operating room to where the block is prepared, something has gone wrong to affect the quality of the tissue?
DR. MULLEN:
A. Has gone wrong, yes.
MR. SIMMONS:
Q. Even though ultimately you were able to report it?

Page 245

DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. If we look at that same page on exhibit P-1837, which is your table of the slide re-reads, you've pointed out already that there is one entry about two-thirds of the way down where you have NL Mayo Clinic results?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. And what I understand that that must have been an ER/PR test that had been sent out to the Mayo Clinic and reported back to St. John's, to Newfoundland from the Mayo Clinic?
DR. MULLEN:
A. Yes.
MR. SIMMONS:
Q. And I note that the ER and the PR are described in the column there as N and P for negative and positive, rather than with a percentage.
DR. MULLEN:
A. Yes.
MR. SIMMONS:

Page 246

Q. Do I take it that if the Mayo Clinic had reported a percentage, that you would have included it in this table?
DR. MULLEN:
A. I didn't have the original Mayo Clinic report.
MR. SIMMONS:
Q. Okay.
DR. MULLEN:
A. All I had was the comment that these tests were done at the Mayo Clinic and negative, positive, so I really have no idea what the Mayo Clinic said.
MR. SIMMONS:
Q. Good, okay. Now I take it that this was a rather--the retrospective study here was a rather unusual exercise to take out such a large number of blocks from previous years and retest them and compare the results to the original--to the original testing.
DR. MULLEN:
A. Do you mean this study or the -
MR. SIMMONS:
Q. Yes. The retrospective study that you had to do in the sense of being asked -
DR. MULLEN:

Page 247

A. '97 to '05, that study?
MR. SIMMONS:
Q. Yes.
DR. MULLEN:
A. In my experience, well, my limited experience, yes.
MR. SIMMONS:
Q. Have you, I mean, you've been a pathologist for quite some time and involved in this area and you're located at an institution which is well renown for its involvement in research and so on. Have you heard of anything like this being done anywhere before?
DR. MULLEN:
A. I've heard of it since we initiated this, there is a number of reviews going on across the country, but not specifically for ER/PR.
MR. SIMMONS:
Q. Uh-hm, right. But prior to this were you aware of any, even scientific study that anyone carried out to look back at ER/PR test results from previous years and retest them with current standards and technology and determine what the results would be?
DR. MULLEN:

Page 248

A. I'm not.
MR. SIMMONS:
Q. Because if we look at the article that you were referred to a short time ago, P-1767 please? This is the Goldstein article from 2007.
DR. MULLEN:
A. Uh-hm.
MR. SIMMONS:
Q. And the beginning of the abstract says that "immunohistochemistry continues to suffer from variable consistency, poor reproducibility, quality assurance disparities and the lack of standardization resulting in poor concordance, validation and verification." Which seems to be a fairly blanket statement about these sorts of problems continuing to exist in the year 2007 in this field. And I wonder, I mean, you've read through the whole article, I'm sure, and reviewed it. What is your understanding of what the authors are suggesting here? Are they suggesting that these are problems narrowly confined or of more wide spread concern?
DR. MULLEN:

Page 249

A. They're wide spread concern. Most of these refer to reproducibility between laboratories, quality assurance disparities, the--within a laboratory one would expect that the laboratory had established the criteria for performing both fixation, processing and staining.

MR. SIMMONS:

Q. But to state that there's a problem with reproducibility between laboratories, am I not correct that that suggests that the same specimen tested in two different laboratories could produce two different results?

DR. MULLEN:

A. Certainly.

MR. SIMMONS:

Q. And that that's, according to this article, a recognized problem in the field that still exists in 2007?

DR. MULLEN:

A. Yes, oh yes.

MR. SIMMONS:

Q. Thank you very much, Dr. Mullen, that's all the question I have for you.

THE COMMISSIONER:

Page 250

Q. Mr. Browne?

DR. BRENDAN MULLEN, EXAMINATION BY MR. PETER BROWNE

MR. BROWNE:

Q. Dr. Mullen, we met yesterday, I'm Peter Browne. Just a couple of questions, actually Mr. Simmons has covered a number of the areas that I was going to ask you about. Just toward the end of Mr. Coffey's questioning of you today, he asked you about in-house formalin and I think you, the preparation of in-house formalin, I thought I recalled some discussion about preparation or you referenced formalin preparation.

DR. MULLEN:

A. Yes, it was not uncommon in the 70's, 80's and 90's for departments to prepare their own formalin.

MR. BROWNE:

Q. Yes.

DR. MULLEN:

A. So there were issues with standardization and all of those sorts of things. But I believe in the late 90's going forward, I can't speak for other laboratories, but the majority of laboratories buy commercially prepared

Page 251

formalin, 20 litre packages.

MR. BROWNE:

Q. Was it brought to your attention that in some of the labs here in Newfoundland that that practice may not have stopped until 2003?

DR. MULLEN:

A. I better explain, the only information I have about the Newfoundland practices--or I should say that I had with Newfoundland practices, was I had a block going forward, I had no information on the individual laboratories, that was not--I was not informed of that and I wasn't, as I mentioned, I wasn't privy to Ms. Wegrynowski's report until it was published.

MR. BROWNE:

Q. With regard to the issue of, and you said in the 90's, that's late 90's that that stopped or -

DR. MULLEN:

A. Certainly we stopped it, I can't give specific dates.

MR. BROWNE:

Q. And I guess the point you're making with regard to in-house formalin is that if no standards are in place for the preparation of

Page 252

that, that may affect fixation?

DR. MULLEN:

A. Certainly, certainly, that would be a major contributor.

MR. BROWNE:

Q. A major contributor?

DR. MULLEN:

A. That could be a major contributor if you have unstandardized formalin, if it's not ten percent neutral buffered, then that could be--that's the keystone to the fixation process and if you don't fix, then everything else is suspect.

MR. BROWNE:

Q. Okay. The term "low expresser" it's in relation to--I've read this in the literature about in relation to ER, is that a term that you're familiar with in pathology?

DR. MULLEN:

A. Expresser -

MR. BROWNE:

Q. Low expresser tumor.

DR. MULLEN:

A. That would probably have not--low expresser sounds like a person than a tumor, but -

Page 253

MR. BROWNE:
Q. At least it's not a term that you're familiar with?
DR. MULLEN:
A. No, low positive and positive are the terms I've used.
MR. BROWNE:
Q. Okay, so that it may in fact, you may use different terminology with respect to positivity?
DR. MULLEN:
A. Yes.
MR. BROWNE:
Q. Okay, in terms of low, high -
DR. MULLEN:
A. Low positive or positive, yes. I mean, institutions vary with their terminology.
MR. BROWNE:
Q. And just moving from there into, you spoke about internal and external controls, if you used high expresser or high positive tumor as your external control, could that stain stronger than the internal control?
DR. MULLEN:
A. Yes.

Page 254

MR. BROWNE:
Q. And I think you mentioned this morning and Ms. Wegrynowski when she testified the other day also mentioned about this instrument, the microtome and I think you were shown a number of client referral forms that you use in your institution about comments about, from the lab about -
DR. MULLEN:
A. The client satisfaction.
MR. BROWNE:
Q. Yes, and one of those referenced and I just want to, I think, point about trimming the tissue.
DR. MULLEN:
A. Yes.
MR. BROWNE:
Q. And because of the trimming there was a loss of tissue, did I understand?
DR. MULLEN:
A. No, they didn't trim because there was so little tissue, they didn't want to lose the tissue.
MR. BROWNE:
Q. Okay.

Page 255

DR. MULLEN:
A. Do you want my graphic description with my Kleenex box?
MR. BROWNE:
Q. No, that's fine, you've explained that, so in terms of the layers--sure, I mean, if you wish, go ahead.
DR. MULLEN:
A. All right, this is essentially a block, it's paraffin wax with a tissue in it and put on plastic, a plastic container. It's put in a microtome which basically is the equivalent of a razor blade that moves sequentially, you can either have an automated or manual. Blocks, the paraffin wax is not necessarily--sorry, the paraffin wax is not necessarily flat and the embedding of the--or the position of the block is not always perpendicular to the microtome. So what happens is that if there's sufficient tissue there, the technologist will do a few cuts to get a flat face and then will do a--what you're basically trying to get at is a complete section of the tissue. But if there's very little tissue and they can see that through the depth of the tissue, they

Page 256

will not trim, they will just take whatever--they'll take sequential sections and use those. So that's what that's referring to.
MR. BROWNE:
Q. And again, staying with the issue of internal controls, are there instances where it is, I guess, not possible to get an internal control?
DR. MULLEN:
A. Certainly.
MR. BROWNE:
Q. Can you explain to the Commissioner those examples?
DR. MULLEN:
A. Well first of all the major group are patients who have metastatic carcinoma, that's breast carcinoma that has been removed, that's involved either a lymph node or other portions of the body that you would not expect to have breast tissue, obviously in a lymph node or breast tissue in a lung, so the absence of internal controls there would be certainly quite acceptable. And if you had internal control, you would worry. The next set of cases are, as I mentioned, in post menopausal

Page 257

patients, there's atrophy of the normal breast and you may, the likelihood of having an internal control would decrease with age.

MR. BROWNE:

Q. Okay.

DR. MULLEN:

A. So it's a selection issue.

MR. BROWNE:

Q. And is it sometimes difficult in core biopsies as well to obtain internal control?

DR. MULLEN:

A. Again, if it's pre menopausal verses postmenopausal.

MR. BROWNE:

Q. So it depends on pre and the post?

DR. MULLEN:

A. Yes, yes, that would be one of the major, plus if the core biopsy contains normal breast tissue or it contains tumor only.

MR. BROWNE:

Q. Okay, and then the issue about core biopsies that has been talked about a lot in the literature, in terms of results and problems with obtaining ER results, is that -

DR. MULLEN:

Page 258

A. No, you can obtain ER results, one of the issues with the core biopsies is the representation of the tumor. Mr. Simmons alluded to the fact that there is variability from area to area, so if you get an area that is low, verses an area that is high, what we try to do is maximize the amount that we assess.

MR. BROWNE:

Q. And just moving now to your Mount Sinai in terms of the quality control, dealing with your in-house slides, do I understand from your evidence and Ms. Wegrynowski's evidence that if there's a concern with the quality of a slide, that there is a lead technician who a pathologist can go to and make complaints?

DR. MULLEN:

A. Yes, Ms. Wegrynowski is the -

MR. BROWNE:

Q. Is that person?

DR. MULLEN:

A. Yes, is that person. And there's also a medical head.

MR. BROWNE:

Q. And finally you mentioned this afternoon about

Page 259

the notion of bi-modal distribution and as a matter of fact, several preceding witnesses talked about that, that entity, was that just recently, a recent sort of recognition in literature? There was an article that was put in through one of the witnesses around, came out around 2005 that this wasn't really known before then?

DR. MULLEN:

A. I can't speak to that.

MR. BROWNE:

Q. That's all the questions I have, Commissioner. Thank you, Doctor.

THE COMMISSIONER:

Q. Mr. Eaton?

EATON, Q.C.:

Q. No questions, thank you.

THE COMMISSIONER:

Q. Now, do you have any questions, just looking at the clock in terms of taking the break and I'm wondering if it would be better if we took the break before you started questioning, assuming you have any.

MS. NEWBURY:

Q. I probably have about twenty or twenty-five

Page 260

minutes.

THE COMMISSIONER:

Q. Why don't we take the afternoon break.

(RECESS)

THE COMMISSIONER:

Q. Please be seated. Ms. Newbury.

DR. BRENDAN MULLEN, EXAMINATION BY MS. JENNIFER NEWBURY

MS. NEWBURY:

Q. Good afternoon, Dr. Mullen. Jennifer Newbury for the Canadian Cancer Society, Newfoundland and Labrador division. I have a few questions for you this morning (sic). First of all, I just wanted to ask you a little bit about the choice to use the research laboratory facilities at Mount Sinai, as opposed to your regular services, and do I understand it correctly that that was done for a couple of reasons: one being the capacity issues and second, it would also make it unnecessary for you to do a report in each case.

DR. MULLEN:

A. The capacity issue, yes. No, the report issue, I could have issued a report on the research services side, that was at the, I believe in discussions with Eastern Health,

Page 261

part of it was my understanding of the Public Hospital Act in Ontario, whether it was applicable or not in Newfoundland is--you can discuss with, well you're a lawyer here, obviously. Whether the report then would have to go to the patient's chart, well my understanding when I initiated this whole process, the 50 to 100 that I was doing, that it was a retrospective sort of, not a research, but a look back and it was time limited in a few cases and this would be the fastest and most effective way. And what my expectation was that the hospital would then review, the pathologist would then review my interpretation and deal with it that way.

MS. NEWBURY:

Q. Okay, so you were aware then that ultimately the work that you were doing would have been reflected in the patient's chart and that was being done for the purposes of patient care?

DR. MULLEN:

A. Not initially, but once we were into the process, then, yes.

MS. NEWBURY:

Q. Okay, at what stage did you understand that it

Page 262

was ultimately going to be for the purposes of patient care? Was it fairly early on in the process? When you realized that you were not just doing 50 to 100 cases, that you were -

DR. MULLEN:

A. When it started, yes, and especially when there was the request and I can't give you the exact dates, the request to pull things out to actually diagnose them for--and to issue a formal report.

MS. NEWBURY:

Q. Okay, so if you had any doubts before as to whether or not this was being done for patient care, that's what clinched it for you.

DR. MULLEN:

A. Yes, but from my point of view, other than the capacity issue, the interpretation would have been exactly the same, it's just a format of the report.

MS. NEWBURY:

Q. Sure, okay. And you are aware then that all of those reviews that you did for the retrospective review was ultimately for the purpose of patient care, even though you may not have known that from the very beginning.

Page 263

DR. MULLEN:

A. Not initially, yes.

MS. NEWBURY:

Q. And were you ever told that any of the retrospective testing would be done for the purposes of peer review or quality review and therefore, subject to any sort of special privilege based on those categories?

DR. MULLEN:

A. No, you've seen the e-mails, those are fairly inclusive, certainly includes everything that I was aware of.

MS. NEWBURY:

Q. Okay.

DR. MULLEN:

A. And as I mentioned yesterday, I was always the last to know. We would commit to things and you have to do it.

MS. NEWBURY:

Q. Okay. And would you have expected that internal quality control procedures for a laboratory medicine program would have detected the types of fixation and processing problems that you were observing when you were doing the retesting?

Page 264

DR. MULLEN:

A. Sorry, could you be--the beginning of your sentence, the laboratory internal quality?

MS. NEWBURY:

Q. Internal quality control procedures that you would--that you would have, for example, at Mount Sinai, would those have detected the types of fixation and processing problems that you were observing?

DR. MULLEN:

A. Yes, I would certainly expect that.

MS. NEWBURY:

Q. Okay. And would you have also -

DR. MULLEN:

A. I mean, you have to be very careful about using the term "quality control", I mean, when we talk about quality control and the statistics, I mean, those are fine, but it's each day, each case, each pathologist, that's the main quality check. Before they put their name on anything, they want to ensure that it is of the highest standard, so to say that you hide it under quality control, it's the individual pathologist who is ultimately responsible, so they should act at the time

Page 265

the specimen reaches their desk. So individual, yes, and then if you want to call the overall process of quality control, but case by case by case.

MS. NEWBURY:

Q. Right, but you do in fact have -

DR. MULLEN:

A. Yes.

MS. NEWBURY:

Q. Or you would expect to have on each and every case a quality control procedure that you're following for each individual case? And perhaps I'm not clear on the distinction between quality control and quality assurance.

DR. MULLEN:

A. Okay, well quality assurance is, in broad terms is a professional, that you're making sure that the interpretation is the same. Quality control is the, for the simple terms, is the technical, that each step is controlled. But if you're talking about a program, it's more that we compile figures and we take our client satisfaction sheets, that type of thing.

MS. NEWBURY:

Page 266

Q. Right, looking at your statistics as an example.

DR. MULLEN:

A. Yes, but when I'm talking about the quality issue, it's the pathologist on that slide before they put their name on it, that everything has to be in place.

MS. NEWBURY:

Q. Okay. And if you had those internal procedures in place, they would detect it, in theory, on each and every slide as they're being reviewed?

DR. MULLEN:

A. Yes, because it's the individual pathologist, yes.

MS. NEWBURY:

Q. So contemporaneously really with reading of those initial slides, if you had the internal quality control procedures in place, that, in theory, ought to have detected each of these problems as they occurred or shortly after?

DR. MULLEN:

A. Yes, well going back to my lovely little comment yesterday, one, maybe, two, "umph", and three then -

Page 267

MS. NEWBURY:

Q. Sure.

DR. MULLEN:

A. I mean, that's the key. I mean, you can have one-offs, we know that, one-offs, but if it's repeated, then it's time to act and in my institution, two is possible, three is we act.

MS. NEWBURY:

Q. And in addition to those internal quality controls, you would expect that external quality assurance programs, and I believe there are a variety of programs available -

DR. MULLEN:

A. Yes.

MS. NEWBURY:

Q. You would have expected that those programs, had they been in place and utilized, that they would have detected the types of fixation and processing problems that you had seen?

DR. MULLEN:

A. No, the quality control or the quality assurance--well quality control yes, QMPLS we send our material. When I say QMPLS, Quality Management Program Laboratory Services in Ontario, yes, we send. The quality assurance

Page 268

programs, slides are sent to us, we stain an we interpret, no. So that would not pick up the fixation processing issue. QMPLS would.

MS. NEWBURY:

Q. Okay.

DR. MULLEN:

A. QMPLS is a technical, okay, so QMPLS they're basically, when we're talking about the pathology laboratory, there are patterns of practice which are essentially surveys and when I alluded to the 1866, the last QMPLS survey on HER2 was how many did you do, so ran my stats, 1866. There are, so that's pattern of practice, the other is interpret--well, it's not really interpretative, cytology slides we issue a diagnosis, they're more of, because of legal restrictions, they're not--we make a diagnosis but it's not attributed to any one person, it's laboratory. And then there are the technical, but they will send you a specimen, you stain it or you send slides that you've processed and stained and they evaluate them. So that's the technical side.

MS. NEWBURY:

Page 269

Q. That's the distinction. So then you've got both external quality control and external quality assurance programs available.
DR. MULLEN:
A. Yes, yes, that's correct.
MS. NEWBURY:
Q. And QMPLS is considered to be an external quality control.
DR. MULLEN:
A. Yes, quality management, yes.
MS. NEWBURY:
Q. And you UK NEQAS program would be external quality assurance?
DR. MULLEN:
A. Both.
MS. NEWBURY:
Q. They have both programs.
DR. MULLEN:
A. Yes.
MS. NEWBURY:
Q. And do you sign up for one or both?
DR. MULLEN:
A. No, I think it's included, Mr. Simmons was saying they assess your staining, then that would be the quality control and the quality

Page 270

assurance is we make the diagnosis.
MS. NEWBURY:
Q. Okay.
DR. MULLEN:
A. But I stand to be corrected on that.
MS. NEWBURY:
Q. Okay, so you think then if you had external quality control programs in place, then that could have detected the types of fixation and processing problems that you were observing.
DR. MULLEN:
A. May have.
MS. NEWBURY:
Q. May have, okay, so really the key would be the internal quality controls.
DR. MULLEN:
A. Yes.
MS. NEWBURY:
Q. That's the first and foremost program that you look it.
DR. MULLEN:
A. Yes, everything is done--initial is your, I mean, it's a canary in the mind, you have something internal.
MS. NEWBURY:

Page 271

Q. Sure. I wonder if I could have exhibit P-0144 please? This is an e-mail that you weren't involved in, but I just wanted to refer you, it's an e-mail between George Tilley and Carolyn Chaplin, it's actually an exchange on October 19th, 2005. George Tilley was the CEO of Eastern Health at the time.
DR. MULLEN:
A. And Carolyn Chaplin -
MS. NEWBURY:
Q. And Carolyn Chaplin was in communications for the province at that time.
DR. MULLEN:
A. Okay, Government of Newfoundland, okay.
MS. NEWBURY:
Q. Yes, for the Government of Newfoundland, she was previously involved with the Department of Health, but had moved positions by this time and I'm not going to lead you through the details on that unless you want to look at it, of course. There's one comment here that I wanted to ask if you're familiar with and that's towards the bottom of the page and it's the, I guess technically it's the fourth last paragraph in the e-mail and it starts, "I have

Page 272

talked to the CEO of Mount Sinai to see if we can expedite the retesting process."
DR. MULLEN:
A. Sorry, can I see the date of this? Sorry, I'm just trying to put it in -
MS. NEWBURY:
Q. Yeah, they're October 19th. Put it in context, sure.
DR. MULLEN:
A. Yes, what pressures.
MS. NEWBURY:
Q. So those, the original e-mail and the response are both on the 19th of October, 2005. And here in the fourth last paragraph--and if you want to take your time and go through it, but I'll show you the key paragraph first -
DR. MULLEN:
A. No, that's fine.
MS. NEWBURY:
Q. "I have talked to the CEO of Mount Sinai to see if we can expedite the retesting process. I have also started investigating where we can put this issue nationally, since this appears to be more than a local problem. One of my CEO colleagues in Ontario, who is also an

Page 273

oncologist, told me earlier tonight it is gray test." And he's talking generally in this e-mail, as I understand it, about ER/PR testing, so I think that the reference to gray test is a reference to the ER/PR testing. And I just want to ask did anyone at Eastern Health ever discuss this concept with you about whether or not this is considered to be a gray test, that terminology?

DR. MULLEN:

A. No, I've never heard that term.

MS. NEWBURY:

Q. Okay, ever, not from anyone -

DR. MULLEN:

A. Not from anyone, no. I mean, it's a brown test, but it's not a gray test, yes.

MS. NEWBURY:

Q. And you mentioned earlier this morning that pathology isn't black and white.

DR. MULLEN:

A. No, and I flippantly said brown and white but there's an art to it and a science to it.

MS. NEWBURY:

Q. Right, okay. And had you been asked about this at the time, would you have agreed with

Page 274

the characterization there of ER/PR testing to be a gray test?

DR. MULLEN:

A. No, I would not.

MS. NEWBURY:

Q. And why not?

DR. MULLEN:

A. My understanding is--gray test--if we follow the recommendations that were in the, for standardization, I mean, internally you have the same fixation, if you optimize everything, then your reproducibility should be quite high.

MS. NEWBURY:

Q. Okay.

DR. MULLEN:

A. And I'm not sure if the gray test is, they're referring to reproducibility or whether the interpretation of it, so whether it's of value to anyone, I'm not sure.

MS. NEWBURY:

Q. Okay. But in any event that wasn't a concept discussed with you at anytime by anyone at Eastern Health.

DR. MUNDEN:

Page 275

A. Low man on the totem pole, as I mentioned.

MS. NEWBURY:

Q. And did any of your colleagues at Mount Sinai who may have more direct contact with representatives of Eastern Health, did any of those individuals ever discuss this with you?

DR. MUNDEN:

A. I mean, the e-mail, I'm not sure whether it was--most of them - "Where are you on the status?" It's not "Hurry up." It's "Where are you on the status" type of thing.

MS. NEWBURY:

Q. Uh-hm. Okay. You're just updating.

DR. MUNDEN:

A. I mean, it's not as though we were holding them. At that time it was a capacity issue so then that may have been the impetus. I can't suggest it may have been the impetus to buy the machine, validate and go.

MS. NEWBURY:

Q. Uh-hm.

DR. MUNDEN:

A. Okay. CEO's have a unrealistic expectation of the turnaround time for material.

MS. NEWBURY:

Page 276

Q. Okay.

DR. MUNDEN:

A. Snap their fingers and hope for the best, or expect--doesn't happen. There are physical constraints.

MS. NEWBURY:

Q. Okay, thank you. Could I have Exhibit P-0110, please? This is a transcript of a live news conference dated May 18, 2007, and Mr. Tilley is the person who's, for the most part, being recorded here in the transcript.

DR. MUNDEN:

A. Yes, okay.

MS. NEWBURY:

Q. I mean, you can feel free to read the whole thing if you want.

DR. MUNDEN:

A. No, no, I'm just reading what Nancy said, okay.

MS. NEWBURY:

Q. Okay, but I'll refer you to a paragraph on Page 3. You can see a lot of this is just a quote from Mr. Tilley, and again this is during the news conference. Mr. Tilley says here, and it's right there in the middle of

Page 277

the page. "We saw a change in results for 317 patients and, as you point out, there is an element of uncertainty in this particular test and it's quite well known both nationally and internationally. When we first became of this and decided to suspend treatment, our physicians and technologists spent a great deal of time looking inside the organization looking at the procedure for that test. We also sought the input of a technologist and a physician more independent of the organization to come and give us an objective assessment as to what we do and how we do it. I recall that the comments of the physician were that he considered us to be in the middle of the pack in terms of laboratory services with regards to ER/PR." And my question is, were you ever asked by anyone at Eastern Health how its lab compared with other labs in Canada?

DR. MUNDEN:

A. Though may I suggest it might have been Dr. Banerjee.

MS. NEWBURY:

Q. I believe it was.

DR. MUNDEN:

Page 278

A. Yes.

MS. NEWBURY:

Q. Yes, I'm fairly sure that's -

DR. MUNDEN:

A. No, I -

MS. NEWBURY:

Q. Yes, I should have said that.

DR. MUNDEN:

A. This is my second visit to Newfoundland.

MS. NEWBURY:

Q. Yes.

DR. MUNDEN:

A. I have not had the opportunity - and the other one was years ago - I've not had the opportunity to review the lab. I've not been asked to review the lab. That was out of the scope of my involvement in this project.

MS. NEWBURY:

Q. I appreciate that. You had a fairly defined scope of activity.

DR. MUNDEN:

A. Yes.

MS. NEWBURY:

Q. But I guess, you know, even though it may not have been to do a review of the lab itself,

Page 279

you do have some insight, I guess, into what the product or what the results were.

DR. MUNDEN:

A. But it's difficult to, as Mr. Simmons was pointing out through his line of questioning, it's very difficult for me at the end of the day to go back and say whether it was the operating room's issue, the fixation issue, the formalin issue. It's a compilation of all of those and, sitting in Toronto in my office, it's not my--I would certainly be beyond my ability to say it was this, this or this.

MS. NEWBURY:

Q. Right, and I do appreciate that but I guess I'm just curious whether or not anyone ever discussed with you -

DR. MUNDEN:

A. No.

MS. NEWBURY:

Q. Because you would have some insight in terms of what you did see in terms of your retesting.

DR. MUNDEN:

A. Other than my discussion with Dr. Carter and my e-mail to Dr. Cook, no.

Page 280

MS. NEWBURY:

Q. Okay, and no one ever said from Eastern Health, you know, "We understand that we're in the middle of the pack in terms of laboratory services relating to ER/PR, do you agree or what do you think," you know -

DR. MUNDEN:

A. No, no, nobody asked me that question.

MS. NEWBURY:

Q. And if you had asked, would you have been able to give any comment - agree, disagree - just in terms of your role, what you saw with the testing?

DR. MUNDEN:

A. You're asking me to speculate on something I don't feel comfortable doing.

MS. NEWBURY:

Q. Okay.

DR. MUNDEN:

A. Because, I mean, my experience with the ER/PR, I mean, the middle of pack are two of us. There's Mount Sinai.

MS. NEWBURY:

Q. Right.

DR. MUNDEN:

Page 281

A. And Eastern Health. I mean, I haven't gone anywhere else to -
MS. NEWBURY:
Q. Okay.
DR. MUNDEN:
A. So I really - it's not relevant.
MS. NEWBURY:
Q. Okay.
DR. MUNDEN:
A. And I think it's--we're back to our statistics.
MS. NEWBURY:
Q. Right.
DR. MUNDEN:
A. We're at the top, they're at the bottom, if you have two, but it's--I don't really -
MS. NEWBURY:
Q. You don't have enough information about what other labs are doing.
DR. MUNDEN:
A. I don't have anybody else, and I certainly don't have anybody above us.
MS. NEWBURY:
Q. Yes.
DR. MUNDEN:

Page 282

A. I'm not suggesting we're the top, but of two what's middle of the pack, I don't know.
MS. NEWBURY:
Q. Right. Okay. So you don't have another -
DR. MUNDEN:
A. No.
MS. NEWBURY:
Q. Enough information about the rest of the pack, basically.
DR. MUNDEN:
A. No.
MS. NEWBURY:
Q. Okay.
DR. MUNDEN:
A. I mean, let's be honest.
MS. NEWBURY:
Q. Yes.
DR. MUNDEN:
A. You need three numbers for mean standard deviation.
MS. NEWBURY:
Q. Sure.
DR. MUNDEN:
A. If numbers--average mean standard deviation -
MS. NEWBURY:

Page 283

Q. Okay.
DR. MUNDEN:
A. You can't do that on this. I'm not going to be flippant, but I just don't know.
MS. NEWBURY:
Q. Yes. No, that's fine. If I could have Exhibit P-0104, please? This is another document that you're probably not familiar with. This is an e-mail from a communications person from Eastern Health to a communications person with the Department of Health, and it attaches materials for a technical briefing that was held by Eastern Health in December of 2006, and I just wanted to refer you to a couple of comments in that technical briefing. Page 31, please, and what is set out here are some questions and answers that Eastern Health had prepared, and I understand would have been referenced during the technical briefing, and just scroll down to the bottom of the page. Question number 12, right here in the middle, it's asking, "Were there quality checks in place when the error was discovered," and the answer, 12, "All laboratory testing conducted at Eastern Health use the standard controls."

Page 284

Were you asked by anyone at Eastern Health whether or not that would be an appropriate answer to that particular question?
DR. MUNDEN:
A. No.
MS. NEWBURY:
Q. Okay. And if you had been asked, would you have been able to agree, as it relates to what you saw with ER/PR testing? Obviously, you can't talk about everything that happened at Eastern Health.
DR. MUNDEN:
A. No.
MS. NEWBURY:
Q. But just from your perspective.
DR. MUNDEN:
A. Of course, I didn't get the negative controls but we stopped doing negative controls.
MS. NEWBURY:
Q. Uh-hm.
DR. MUNDEN:
A. I mean, I had the external controls in the cases that they were available. I can't go beyond that.
MS. NEWBURY:

Page 285

Q. Okay.
DR. MUNDEN:
A. Okay. I mean, again that would be something either Dr. Banerjee or Ms. Wegrynowski could speak to.
MS. NEWBURY:
Q. Okay.
DR. MUNDEN:
A. They actually did site visits.
MS. NEWBURY:
Q. Right, but in the materials that you saw you've pointed out a number of problems with internal controls - quality.
DR. MUNDEN:
A. Yes, yes.
MS. NEWBURY:
Q. And sometimes the complete absence of those controls.
DR. MUNDEN:
A. Yes.
MS. NEWBURY:
Q. And Page 32, which is the next page there, Question Number 14 - and, again, this is referring generally to the problems with the ER/PR testing, so that would include the

Page 286

retrospective testing that you had been involved in. Question Number 14, "Could more have been done to prevent this from happening," and the answer, "This is impossible to answer at this point." And just to remind you, this is December of 2006 that this technical briefing is being held.
DR. MUNDEN:
A. 2006?
MS. NEWBURY:
Q. Yes, so that would be almost a year after you had completed the retrospective testing.
DR. MUNDEN:
A. Are you sure this is '06?
MS. NEWBURY:
Q. Yes.
DR. MUNDEN:
A. Because we reported everything in--was it April of '06?
MS. NEWBURY:
Q. January.
DR. MUNDEN:
A. January of '06.
MS. NEWBURY:
Q. January of 2006, you had the bulk of it done.

Page 287

DR. MUNDEN:
A. So this is eight or ten months later.
MS. NEWBURY:
Q. Yes, that's correct, almost a year later.
DR. MUNDEN:
A. Okay.
MS. NEWBURY:
Q. Okay. First of all, were you asked whether or not more could have been done to prevent this from happening?
DR. MUNDEN:
A. No.
MS. NEWBURY:
Q. By anyone at Eastern Health?
DR. MUNDEN:
A. No.
MS. NEWBURY:
Q. And would you have been able to agree with the answer, had you been asked?
DR. MUNDEN:
A. "Could more have been done to prevent this from happening" - and this is referring to everything -
MS. NEWBURY:
Q. The problems with the ER/PR testing.

Page 288

DR. MUNDEN:
A. I would suggest if the proper--not proper - if standardized handling, fixation, processing had been in place - I can't speak to the immunohistochemistry. I think Ms. Wegrynowski did that report.
MS. NEWBURY:
Q. Uh-hm.
DR. MUNDEN:
A. But based on what I was receiving, if there were standard handling, fixation and processing, it might have helped to minimize. I can't speak to the rest.
MS. NEWBURY:
Q. Sure. I just wanted to ask you to explain something I was a little bit confused about yesterday, and I want to try to reconcile in my mind a couple of comments that you made. One of your comments, and you have indicated this a couple of times now - you had indicated that if there was material present--or if this material was present, the type of material that you were seeing in the retesting, the problems with the handling, fixation and processing -

Page 289

DR. MUNDEN:
A. Uh-hm.
MS. NEWBURY:
Q. Then you might be able to tolerate one, the second -
DR. MUNDEN:
A. That's the issue - would you wait for statistics?
MS. NEWBURY:
Q. Right.
DR. MUNDEN:
A. Or do you act on what the issues are?
MS. NEWBURY:
Q. Yes.
DR. MUNDEN:
A. Right?
MS. NEWBURY:
Q. And by case number three, you'd act.
DR. MUNDEN:
A. Yes.
MS. NEWBURY:
Q. Okay.
DR. MUNDEN:
A. As I expressed.
MS. NEWBURY:

Page 290

Q. Yes. And you had also indicated when you were discussing this concept of not acting, not waiting for your states, but acting on case number three.
DR. MUNDEN:
A. Yes, we might act on two or even one but -
MS. NEWBURY:
Q. Right. Sure.
DR. MUNDEN:
A. Yeah.
MS. NEWBURY:
Q. But certainly by three the red flag is there and you're going to take action.
DR. MUNDEN:
A. Yes.
MS. NEWBURY:
Q. And you had also mentioned while you were discussing that that what's affecting the breast tissue is also affecting other specimens that are being received, so it's not something you would see in isolation.
DR. MUNDEN:
A. No.
MS. NEWBURY:
Q. Now I think you explained in further detail

Page 291

this morning that some other testing may not susceptible to the types of--you might be able to work better with problematic specimens.
DR. MUNDEN:
A. Yes.
MS. NEWBURY:
Q. In terms of fixation processing more so than with the breast specimens.
DR. MUNDEN:
A. Yes.
MS. NEWBURY:
Q. But you would be seeing these types of slides over and over in other specimens aside from breast tissue?
DR. MUNDEN:
A. That's correct. Okay.
MS. NEWBURY:
Q. So that's one comment that I wanted to just consider.
DR. MUNDEN:
A. To correct, oh yes.
MS. NEWBURY:
Q. And to compare it with another comment that you made that there are very few pathologists who had the opportunity to review the number

Page 292

of cases that you've reviewed, both prospective and retrospective, and what is inherently obvious to you if you're looking at something for the first time or if you see a case a month, it may not be as obvious to another pathologist. So if you were a pathologist in a routine service and you just see something sort of sporadically, you may not have the same level of alertness as to a potential problem.
DR. MUNDEN:
A. Yes.
MS. NEWBURY:
Q. And I guess what I'm trying to reconcile is if you have fixation and processing for specimens other than breast tissue, would you not expect the pathologist to see these types of things more often and be alert to the problems even though they're in a routine pathology service?
DR. MUNDEN:
A. Yes. It's particularly magnified in breast tissue or any tissue that has a lot of fat in it because fat is very difficult to fix and if you're not necessarily sectioning it.
MS. NEWBURY:

Page 293

Q. Uh-hm.
DR. MUNDEN:
A. The other types of specimens - basically, it would be small specimens. Biopsies would go into formalin, would fix nicely. If there's a processing issue, then the pathologist may pick that up but, if it's mainly a handling and fixation, it's large specimens. So the large specimens that one routinely gets are bowels, and those hospitals routinely open.
MS. NEWBURY:
Q. Uh-hm.
DR. MUNDEN:
A. So they're not enclosed, so the formalin would penetrate quite nicely. The adipose tissue around the bowel may not fix well.
MS. NEWBURY:
Q. Uh-hm.
DR. MUNDEN:
A. Uteri, those are opened, standard opening, so the processing there--the protocols that are usually in place would tend to mitigate against the issue as obvious as you see in breast.
MS. NEWBURY:

Page 294

Q. Okay.
DR. MUNDEN:
A. But the same sort of issue, the fixation.
MS. NEWBURY:
Q. Right. So even though the consequences may not be the same in terms of it interfering with your ability to stain and to read those results -
DR. MUNDEN:
A. Uh-hm.
MS. NEWBURY:
Q. Would it still give an opportunity for the pathologist to become familiar with the types of fixation and processing problems?
DR. MUNDEN:
A. Yes. Across the board, as I said, there's nothing special about the fixation and processing of breast. The only variation from other tissues is that--depending on age, tends to be more fat than other specimens.
MS. NEWBURY:
Q. Okay, thank you. Now you've explained in some detail about the monitoring that you do yourself in terms of the positivity rates of ER and PR. Do you do any other types of

Page 295

monitoring as detailed a fashion as you do with the positivity rates, and some of the other things that I'm thinking about are the positivity by type of cancer, by grade of cancer, anything else. Do you keep any stats on that?
DR. MUNDEN:
A. No. I mean, I can do it but it's not something I do routinely.
MS. NEWBURY:
Q. Okay. And does anyone at your laboratory do that?
DR. MUNDEN:
A. No. You mean, in breast? No, no.
MS. NEWBURY:
Q. Not the breast at all?
DR. MUNDEN:
A. No.
MS. NEWBURY:
Q. Okay. And is that something that the cancer registry is involved in, would you know? Do they keep that sort of information?
DR. MUNDEN:
A. In Ontario every cancer report is sent to the registry and it's done in real time, the

Page 296

minute it's signed it goes, and I don't know what they do with the data.
MS. NEWBURY:
Q. Okay.
DR. MUNDEN:
A. I mean, there are quality indicators in Ontario that are published, a completeness of reports.
MS. NEWBURY:
Q. Uh-hm.
DR. MUNDEN:
A. And it's basically filling in the synoptic report of what they actually do with that type of material, that may be research more than a diagnostic.
MS. NEWBURY:
Q. Okay, how they manipulate the material.
DR. MUNDEN:
A. Yes. I mean, we're in the infancy of quality management in Ontario for this sort of thing.
MS. NEWBURY:
Q. Okay. Do you know the types of information that will be included in the reports relating to ER/PR or breast specimens.
DR. MUNDEN:

Page 297

A. Yes, well, breast specimen, if you're aware, the College of American Pathologists, their guidelines -
MS. NEWBURY:
Q. Uh-hm.
DR. MUNDEN:
A. The College of American Pathologists, a large organization with a lot - we are accredited by the College of American Pathologists. The Pathology Community of Ontario in collaboration with Cancer Care Ontario has entered into--or is in the process of entering into an agreement with the College of American Pathologists who use on a formal basis their checklist.
MS. NEWBURY:
Q. Uh-hm.
DR. MUNDEN:
A. As the gold - I won't call the gold standard - as a standard of reporting in Ontario. There are five sites that are mandatory at the moment and we're rolling them out, increasing the numbers. We in Ontario, because we have one cancer agency -
MS. NEWBURY:

Page 298

Q. Uh-hm.
DR. MUNDEN:
A. Very different than the Americans, and so they will have access to cancer data on four million people, both diagnosis and treatment. So we have a system in Ontario in the major hospitals that are called PIMS, Pathology Information Management System, basically real time in our hospitals - sends the data to Cancer Care Ontario. Other hospitals, depending on their computer system, are batched at the end of the day, batched at the end of the month, and those four institutions that don't have a lab information system, I think most of us have now, send the reports manually.
MS. NEWBURY:
Q. Okay.
DR. MUNDEN:
A. And they're extracted, and so all of the mandatory spots on the cancer checklist are captured. And we are evaluated for our completeness. Now, just--quality management in pathology--can I deviate for just a second?
MS. NEWBURY:

Page 299

Q. Sure.
DR. MULLEN:
A. Quality management in pathology in Ontario, we have--just before I came on Tuesday--I'm the chair of the section Laboratory Medicine of Ontario Medical Association. I'm also secretary of the Ontario Association of Pathologists. I wear multiple hats. So the OAP, the OMA has joined with Quality Management Program, Laboratory Services, and Cancer Care Ontario to devise a strategy to ensure quality management in Ontario, and we've--and we haven't officially adopted the term, but it's quality 4, F-O-U-R, or the number four for pathology because of the four organizations. We are in the process--we realize there is a--well, I won't say a crisis of confidence, but there is unsettled--the population in Canada and in Ontario, because of two incidents, has concerns about quality in laboratory medicine. So we are trying--we are in the infancy, these four organizations which represent the profession and Quality Management represents the--it's a joint Ministry of Health, OMA organization that

Page 300

accredits laboratories. We are trying to develop processes to ensure quality.
Now when we talk--what we're referring to at the moment, when we're talking about--I'm just going to talk about surgical pathology quality management. There are completeness, the four issues in quality management for pathology reports: completeness of the report, so we're talking about the checklist, and that we can do through Cancer Care Ontario; the timeliness, basically a report three years after the fact is of no value, so it's the timeliness, the turnaround time; completeness, timeliness; the accuracy, we have no way at the moment of doing the accuracy, so if I diagnose grade one and it's grade two, that's type of thing, those will be under development; and the fourth issue is accessibility , in other words, if I have a report, but it goes in the mail and nobody can access it, it's not very useful to anyone. So that's--so the four key points for laboratory medicine in our quality management program are those four, timeliness, accuracy, completeness and accessibility, and we're doing--we're

Page 301

initially doing cancer because we have Cancer Care Ontario as a collaborator and once we've developed guidelines for that, we'll then move out from there.

MS. NEWBURY:

Q. Okay. So then in terms of the category number one, completeness -

DR. MULLEN:

A. Yes.

MS. NEWBURY:

Q. And having forms that have all of the recommended -

DR. MULLEN:

A. Required.

MS. NEWBURY:

Q. - required -

DR. MULLEN:

A. Required, they're mandatory and I'm not sure of the term, voluntary. Sorry, I can't--mandatory and optional.

MS. NEWBURY:

Q. Okay.

DR. MULLEN:

A. That go in. Part of the mandatory, when I was talking about the surgical pathology

Page 302

requisition is it's nice to know that it's a breast. It's nice to know which side, but one of the fields that they have, they being the College of American Pathologists, is quadrant, so upper, outer, lower and inner, the four of them, upper, outer, but anyway, it's quadrants, and those of you who--well, nobody here practices medicine, that is never complete. So our standard, we used to be tagged as, you know, deficiencies. Well, we now put in not specified, that type of thing. So pathology is a collaboration between the surgeon or the clinician and the pathologist. If they don't give us any information, it's very difficult to give them the appropriate report. So this is our attempt, infancy at the moment, to develop a quality management that deals with this.

MS. NEWBURY:

Q. And do you envision that all of this information, the mandatory information that will be included in the report, would be passed along to the Cancer Registries?

DR. MULLEN:

A. Oh, it's grabbed automatically. It has to be

Page 303

there or it shows the deficiencies and the CEOs, there's a Cancer Wait Time Strategy in Ontario and the funding for cancer, I mean, that we--has been given to hospitals and they have to sign accountability agreements and one of the accountabilities is that you will report synoptically. So that's the carrot and the stick, and supposedly, the money will come to pathology, but as you know, or those of you in administration, it never comes to pathology. It goes somewhere else.

MS. NEWBURY:

Q. Thank you. I just wanted to ask a little bit more about what's been called retroconverters and that's the--that's a term that's been used here for results that were -

DR. MULLEN:

A. For the seven cases?

MS. NEWBURY:

Q. - were positive that were converted to negative.

DR. MULLEN:

A. Yes.

MS. NEWBURY:

Q. And I'm just wondering if your retrospective

Page 304

review could have--and you'd mentioned this morning that there is a possibility for false positives, hypothetically -

DR. MULLEN:

A. Yes.

MS. NEWBURY:

Q. - to occur, and one of the things that you had identified as a possible contributor to that would be improper validation of antibodies?

DR. MULLEN:

A. Yes, that's correct.

MS. NEWBURY:

Q. Okay, and I'm just wondering if your retrospective review could have detected that type of a problem, if such a problem had existed?

DR. MULLEN:

A. No. It was--if I remember correctly, it was--well, I was--the cases that were selected to be sent to me were the negatives. So 30 or less and then ten and less. So I wouldn't have had anything that was called a positive. Those were not sent to me. So I couldn't do the retroconverters.

MS. NEWBURY:

Page 305

Q. But if some had inadvertently been -
DR. MULLEN:
A. Yes.
MS. NEWBURY:
Q. - included in that group, would you have been able to identify if there was a problem with the validation of the antibodies or was that something outside the scope of what you're looking at?
DR. MULLEN:
A. That would be outside the scope of this review.
MS. NEWBURY:
Q. Okay.
DR. MULLEN:
A. Because, as I said, they were all negatives, and I wouldn't have known the--I didn't know the results to begin with. So that's some -
MS. NEWBURY:
Q. You didn't know the results, okay.
DR. MULLEN:
A. No, that was something that either the Newfoundland authority or whomever is going to analyze the data would be able to speak to.
MS. NEWBURY:

Page 306

Q. Okay. Now I understand that there was a possibility that some ER positives might have been inadvertently included in the group and if that were the case, could you have detected the antibody validation problem or is that something -
DR. MULLEN:
A. Personally, no, because I didn't have the original slide to compare with. I didn't have the result to compare with.
MS. NEWBURY:
Q. Right.
DR. MULLEN:
A. No.
MS. NEWBURY:
Q. Because you were using your own antibodies on those slides?
DR. MULLEN:
A. Yes.
MS. NEWBURY:
Q. Okay. So in that case, you wouldn't have been able to give confirmation or assurances to Eastern Health that there are no issues with that?
DR. MULLEN:

Page 307

A. No, no. Remember, the case selection were negatives, as I found out in December of '07, negatives less than 30 initially and then negatives less than 10.
MS. NEWBURY:
Q. And if you were to delve into that area, if you thought there was any reason to be concerned, you would actually have to look at the original slide?
DR. MULLEN:
A. All positive. No, I'd have to look at the positives.
MS. NEWBURY:
Q. The positives?
DR. MULLEN:
A. Yes.
MS. NEWBURY:
Q. And original slides of the positives or could you -
DR. MULLEN:
A. No, I'd have to do the same thing.
MS. NEWBURY:
Q. Okay, you would have to get blocks and look at -
DR. MULLEN:

Page 308

A. Yes, and do the whole process again, and -
MS. NEWBURY:
Q. And then compare -
DR. MULLEN:
A. - because then I would--what had called a positive would then come out as a zero or less than one or whatever cut off we were using. They do--it would have to be a duplicate study of the positives.
MS. NEWBURY:
Q. Right, and then -
DR. MULLEN:
A. Of what had been positives.
MS. NEWBURY:
Q. And to compare the two results?
DR. MULLEN:
A. Yes, that's correct.
MS. NEWBURY:
Q. And the reason I'm asking you that is I had some information that there were some conversions from--and perhaps just for completeness sake, I can refer you to the Exhibit 0125, page 42. This is an analysis that was done, dated November 23rd, 2006. It's just a brief synopsis of the results of

Page 309

the retesting and there's a number of categories there.

DR. MULLEN:

A. So, sorry, total case, 97, okay, 2760. The 2760 comes from?

MS. NEWBURY:

Q. That's my understanding of the total of the-- they weren't reviewed, but that's the total number of cases that were subject to initial ER/PR testing between '97 and 2005.

DR. MULLEN:

A. Okay.

MS. NEWBURY:

Q. But I understand that -

DR. MULLEN:

A. Oh, okay, so that's -

MS. NEWBURY:

Q. - a small section--that's all of the initial ER/PR testing, so that would include positives and negatives.

DR. MULLEN:

A. Okay, so when we're talking about total cases reviewed, that would be a paper review?

MS. NEWBURY:

Q. Yeah, I'm not--yes.

Page 310

DR. MULLEN:

A. Okay, yes.

MS. NEWBURY:

Q. So that's all of the initial -

DR. MULLEN:

A. So, okay.

MS. NEWBURY:

Q. I don't think Mount Sinai, as I understand it, was involved in that.

DR. MULLEN:

A. No, I think if you look at the next line, the total that were retested would be 939. I'm not sure of the date. Okay.

MS. NEWBURY:

Q. Okay, and I think those numbers might have been, you know, revised upwards, you know, somewhat after.

DR. MULLEN:

A. Results have changed. So basically, they're saying that I've done two-thirds of it, over two-thirds, probably three-quarters by that time, a little over three-quarters, probably 80 percent. No change in results and subsequently no change in treatment, 433. Confirmed negative were 341. Confirmed

Page 311

negative from panel, I'm not sure what that refers to.

MS. NEWBURY:

Q. That would have nothing to do directly with Mount Sinai. There was a panel set up here.

DR. MULLEN:

A. Okay.

MS. NEWBURY:

Q. And I guess the next line is the one, confirmed positive results, and again, I know that it's kind of hard to show you this because the positive, negative definitions were changing over the course of time.

DR. MULLEN:

A. So am I to understand that it was the 12 that would have been less than ten that were greater than ten, is that--or less than 30, greater than 30. Is that what we're referring to?

MS. NEWBURY:

Q. I guess it's the definition of what--people that had been defined to be positive at the time that they were initially tested and it was confirmed as positive upon retesting. That's what I take from this. And then if you

Page 312

scroll down -

DR. MULLEN:

A. And then the DCIS, 52, okay. I'm just going to look at my little cheat sheet. Okay, sorry, I shouldn't use the word "cheat sheet" but my little card, okay.

MS. NEWBURY:

Q. And looking down towards the bottom of the page, next to the cursor here, it says "originally had a degree of ER positivity, but on retesting was negative" and they have four.

DR. MULLEN:

A. Okay.

MS. NEWBURY:

Q. So it appears that there were, if you add the four -

DR. MULLEN:

A. And the 12.

MS. NEWBURY:

Q. - with the 12, that you would have had 16-- what had been defined, I guess by someone, has positive -

DR. MULLEN:

A. Yes.

MS. NEWBURY:

Page 313

Q. - and of those 16, four had converted or were now considered to be negative, and I'm just wondering, can you shed any light on that?

DR. MULLEN:

A. No. There was an exhibit earlier in the day, the retroconverter. Does any--Mr. Browne, you seem to remember all of these exhibits. Do you -

MR. BROWNE:

Q. 1822.

DR. MULLEN:

A. Thank you. Can we see 1822? Sorry, I don't mean to run this, but it just--that was the one with seven, if I'm correct. Is that it? No.

MR. SIMMONS:

Q. Excuse me, Commissioner. Where does this document--these are numbers that Dr. Mullen hasn't seen before. Ms. Newbury has made assumptions about what they mean. I just wonder if there's much value in examining him on these numbers (inaudible).

THE COMMISSIONER:

Q. Well, he's going to tell me if he can't comment on them, I'm quite sure.

Page 314

DR. MULLEN:

A. Okay, sorry, can I--sorry, if this is--okay, all right. That's--this is all I have, and I can't shed any more light on this. All I would know on the retro, and let's see, okay, this is the--and from Dr. Denic, "I would like to thank you"--okay, "seven patients who turned out to be retroconverters." That's--this is all I've been -

MS. NEWBURY:

Q. That's fine, and I'm not expecting you to be able to answer to the numbers there. I just wanted to -

DR. MULLEN:

A. No, this would -

MS. NEWBURY:

Q. - talk to you about the principles and if you had anything, you know, from what you've seen, that could shed any light on any issues that there may or may not be with the ER positive results.

DR. MULLEN:

A. No, all I can speak to is this e-mail and I really can't speak to the briefing note. I'm just not familiar with those numbers.

Page 315

MS. NEWBURY:

Q. Okay, and you weren't involved with testing for ER/PR positive tests?

DR. MULLEN:

A. No.

MS. NEWBURY:

Q. And you can't comment whether or not there were any problems or that there weren't any problems with ER/PR positive tests? That wasn't within the scope of what you were doing?

DR. MULLEN:

A. No, it wasn't within the scope, but I'm not--these are--these were selected, correct me if I'm wrong, these were selected by Dr. Denic and I don't know what criteria they used for me to--I don't know why they thought they were retroconverters. I mean, it would be pure speculation on my part and I don't feel comfortable doing that.

MS. NEWBURY:

Q. No, that's fine. I just wanted to know--basically, I'm trying to find the scope of what you were involved in and what you can or cannot comment upon.

Page 316

DR. MULLEN:

A. Can I just take a second to clarify?

MS. NEWBURY:

Q. Sure.

DR. MULLEN:

A. Okay, the--here we go with my four. Four things, the retrospective review of blocks that had been called negative, less than 30 or less than ten, time periods I'm not sure, 1106 of those blocks. I can't do cases because I wasn't playing with my Excel. So 1106 of those blocks. At the same time, I was involved with the prospective review--I'm sorry, not prospective review, prospective from August 8th of 2005 to today from the three plus variable from St. John's. I was involved starting April of '07, in QA going forward, and also the Commission of Inquiry review of the cases that we discussed this morning, and then this group of seven, I'm not sure whether I included or not, so this would be a fourth category. So that was the scope of my activity. So for the retro review, yes, I knew it was a retroconverter review, because they started it. The going forward, I had no

Page 317

idea whether they were positive or negative, because that was my initial diagnosis. The QA, I had no idea whether they were positive or negative. That was initial diagnosis. And the retro, until I had the meeting with Mr. Simmons, Mr. Coffey, Ms. Chaytor, I had no idea what that was.

MS. NEWBURY:

Q. Okay.

DR. MULLEN:

A. So, and I had no communication with Eastern Health on the scope of these, other than the e-mails that you've seen, and one or two conversations, conversation with Bev Carter that I spoke about, and then the conversations just basically as "where are your slides?" from Dr. Cook. So that, if that clarifies?

MS. NEWBURY:

Q. Yes, it does, thank you.

DR. MULLEN:

A. Sorry.

MS. NEWBURY:

Q. Thank you, those are all the questions I have.

THE COMMISSIONER:

Q. Thank you. Mr. Crosbie?

Page 318

DR. BRENDAN MULLEN, EXAMINATION BY CHESLEY CROSBIE, Q.C.

CROSBIE, Q.C.:

Q. Thank you, Commissioner. Ches Crosbie, Dr. Mullen. I represent the members of the Breast Cancer Testing Class Action, and there's a term "optimizing" that's come up frequently during your testimony and before that. Just to explain that a little bit. Is optimizing something which is optimal--sorry, something which is optional or is it something that you have to do in order to turn out a reliable, acceptable quality of product when you're doing ER and PR stains?

DR. MULLEN:

A. It is mandatory.

CROSBIE, Q.C.:

Q. It is mandatory.

DR. MULLEN:

A. It's not optional.

CROSBIE, Q.C.:

Q. You didn't tell us, when you were speaking earlier, you mentioned that you kept the data to see what the percentages of the positivity percentages were.

DR. MULLEN:

Page 319

A. Yes.

CROSBIE, Q.C.:

Q. On the retrospective cases that you did?

DR. MULLEN:

A. Yes.

CROSBIE, Q.C.:

Q. And you--I don't know if you said you were taken apart, but words more or less to that effect, and then you realized why you were getting the rate that you were getting. Were you able to tell us what the rate was?

DR. MULLEN:

A. Yes. Let me look at my cards. Okay, this is--refers to the 997 blocks that--no, sorry. 997 blocks of--so ER negative--997 blocks, so this is blocks, the cases, some cases will have multiple blocks, so it may not be--it would be certainly less than 997 patients, and this was the data, I believe I presented to--I think it was the December data. So I had 444, which is 44.5 percent were ER negative. ER less or equal to one were 18, which was 1.8 percent. ER -

CROSBIE, Q.C.:

Q. Sorry, give me that again.

Page 320

DR. MULLEN:

A. ER less than or equal to one were 18 which was 1.8 percent, rounding off, basically a thousand is the denominator. ER greater than one to ten, I had 69 cases which is 6.9 and ER greater than ten, I had 466, so 46.7 percent. So, in my classification, I would have ER negative of 46.3, ER positive of 53.7. Using the Eastern Health criteria, I would have 53.2 percent negative and whoever wants to do the mathematics, forty some odd percent of positive. It's easy for me to add 6.9, but 53.7 minus 6.9 is 46.8, I think 46.8?

CROSBIE, Q.C.:

Q. Depending on the criteria, you mean, depending on -

DR. MULLEN:

A. The cutoff point, yes.

CROSBIE, Q.C.:

Q. That's another point I wanted to raise with you for clarification because I think you explained to us that 70 percent of cases will be--I don't know if you were specific to ER or PR or both--I think you said 70 percent of cases will be--sorry, the cases will be 70

Page 321

percent staining, nuclear staining, or better in 90 of cases. Did I have that right?

DR. MULLEN:

A. Yes, that was bi-modal distribution, sorry, in the bi-modal distribution you would have either 0 or greater than 70 in about 99 percent. It's the other one percent that are in between. That's not ER positivity. That's either greater than 70 or 0, less than one. So, that you cannot use to calculate ER/PR rates. The nurses study is the one that we use to calculate -

CROSBIE, Q.C.:

Q. No, but what I'm trying to understand and maybe I'm barking up the wrong tree, but I'm trying to understand the effect of shifting cutoff points from 30 percent to 10 percent to one percent -

DR. MULLEN:

A. That would not be -

CROSBIE, Q.C.:

Q. - on your positivity rate, will it have much affect or will it have really a fairly minor effect? If the distribution of positivity is in the higher ranges -

Page 322

DR. MULLEN:

A. Yes, it shouldn't have much affect.

CROSBIE, Q.C.:

Q. It should not have much affect.

DR. MULLEN:

A. Now, if you read the paper, it is very particular about standardization, fixation, processing and everything has to be optimized. In our cases--I shouldn't say our cases--in the cases that I reviewed, I cannot say that they were optimized. Therefore that paper is the what one should aim for, but if you do the spread, I didn't do the spread in this, there's certainly a lot if you just scan down the list. There were a lot between one and 70.

CROSBIE, Q.C.:

Q. Okay. With that caveat and it may be something to remember by the time I get to the last issue I want to bring up with you which is the actual, the false negative rates in the samples that in the period 1997 through 2005 and also the positivity rates. There's a spreadsheet that I believe you've had a chance to look at, but the essential point here now

Page 323

is that there may be very little effect on the positivity rate, for example, when one considers the change in cutoff points.

DR. MULLEN:

A. You would have to plot the data and recalculate it and I didn't do that.

CROSBIE, Q.C.:

Q. Okay. Well, it may be late in the day for that, but we'll get to that now in a few minutes.

DR. MULLEN:

A. I don't have the sheet here to be able to manipulate the data, but that's something your statistician should do.

CROSBIE, Q.C.:

Q. Or somebody's statistician?

DR. MULLEN:

A. Well, my background is theoretical math, not statistics.

CROSBIE, Q.C.:

Q. Okay. So, anyway, the standard that I gather is being looked for for positivity is somewhere around 78 percent or the high 70s?

DR. MULLEN:

A. The ER/PR, the nurses study is 61.5, the ER

Page 324

positive/PR negative is 15.2. So that, for ER itself would be 76.4 and then ER negative/PR positive, 3.8 percent. So, basically 80 percent, 79, 80 percent, that range.

CROSBIE, Q.C.:

Q. And what does that tell you? If you're looking at your statistics from time to time and you see that you're in that range somewhere or close to it, is that--it's not a guarantee a good quality outcome, it's just one check on it, is that it?

DR. MULLEN:

A. What I've tried to get across, the concept that statistics are nice, but it's the individual case that we live and die on. If my aggregate statistics are fine, but I misdiagnosed or the ER/PR it misinterpreted or on the individual case, that's 100 percent error rate for that patient.

CROSBIE, Q.C.:

Q. Yes, and I think you've done a good job of explaining that and I think I took that point myself. So, it may be useful to know your positivity rate, but it's only one take on whether your process is working well

Page 325

(phonetic).
DR. MULLEN:
A. Certainly, certainly.
CROSBIE, Q.C.:
Q. Did I get from you that you had the feeling that communications were less that optimal with St. John's while this process was going on?
DR. MULLEN:
A. With?
CROSBIE, Q.C.:
Q. Well, in terms of, for example, you being given an opportunity to state to someone in authority such as Doctor Cook the unsatisfactory nature of the materials you were continually receiving.
DR. MULLEN:
A. I had the conversation with Doctor Carter, I mean, we had a very open and frank conversation over a couple of days and reviewed cases together. So, I thought that-- that was certainly one communication. And Doctor Cook, the communication was basically, other than my e-mail about the quality was where are the slides and here are the reports

Page 326

type, that was that -
CROSBIE, Q.C.:
Q. You didn't have the kind of conversation you had with Doctor Carter with him?
DR. MULLEN:
A. No, no.
CROSBIE, Q.C.:
Q. Or with anybody?
DR. MULLEN:
A. That's correct. Now, they were in communication--the lab director may have been in communication with Doctor Pritzker. And I just found out that the CEO to CEO issue--I hadn't heard about that one before.
CROSBIE, Q.C.:
Q. You actually don't know what happened in terms of communication between Doctor Carter, Doctor Cook or anybody else or how good their relations were, do you?
DR. MULLEN:
A. No, beyond the scope of my ability to answer.
CROSBIE, Q.C.:
Q. Also, I got the feeling that you had the feeling that when your reports and whatnot went back to St. John's, that they were just

Page 327

going to rubber stamp it and adopt it as their own, is that correct?
DR. MULLEN:
A. Well, that was my concern, that I would prefer that they actually look at the slides, confirm my opinion and then act.
CROSBIE, Q.C.:
Q. Do you know what they did
DR. MULLEN:
A. No, I don't.
CROSBIE, Q.C.:
Q. Can we bring up that exhibit P-1837 spreadsheet, please. This is something I want to ask you because I just want to understand something here. Just looking right at the item number, it's ID'd number 6 right at the top of that, page -
DR. MULLEN:
A. Yes.
CROSBIE, Q.C.:
Q. - one.
DR. MULLEN:
A. Yes.
CROSBIE, Q.C.:
Q. You've described that as a discordant test.

Page 328

DR. MULLEN:
A. Um-hm.
CROSBIE, Q.C.:
Q. And however, I'm just trying to understand, you got your PRs, 70 and then 90 and your ERs 0 -
DR. MULLEN:
A. And negative.
CROSBIE, Q.C.:
Q. - and negative. Why is that described as discordant? I'm just trying to get a handle on it.
DR. MULLEN:
A. If you recall my--the discordant referred to my Mount Sinai review of the retrospective block. If the value that I reported was present on the pathology report and it varied by one degree, it wasn't in the same category, I would call it discordant.
CROSBIE, Q.C.:
Q. Yes.
DR. MULLEN:
A. So, this is--I agreed with their initial interpretation of the slide, but my review of their retrospective review where we re-stained

Page 329

the block, would of had a different result.
CROSBIE, Q.C.:
Q. Is that visible here?
DR. MULLEN:
A. No, I don't have it on there. What you have to do -
CROSBIE, Q.C.:
Q. Oh, I see, you're relating this information to something that's not on the spreadsheet?
DR. MULLEN:
A. Yes.
CROSBIE, Q.C.:
Q. I see.
DR. MULLEN:
A. My task--I don't have a copy of the letter--but I was tasked to do this and get them back before the end of April.
CROSBIE, Q.C.:
Q. So, to that, when re-stained, according to your lab standards turned out to be discordant?
DR. MULLEN:
A. Yes.
CROSBIE, Q.C.:
Q. I understand.

Page 330

THE COMMISSIONER:
Q. If I understood your evidence this morning, what is NL original and what is MSH review here is that the latter being your opinion based on the same slide that was used in NL original?
DR. MULLEN:
A. Yes, that is correct.
THE COMMISSIONER:
Q. Whereas the comment refers to the slide that you used and produced from a block -
DR. MULLEN:
A. Yes, that is correct.
THE COMMISSIONER:
Q. - in Mount Sinai earlier in the process?
DR. MULLEN:
A. Yes.
CROSBIE, Q.C.:
Q. Just wondering, is there material here for publication or do you intend to publish on any of this?
DR. MULLEN:
A. I have no intention of publishing this. This is not an academic exercise.
CROSBIE, Q.C.:

Page 331

Q. You're the expert, I'm just asking.
DR. MULLEN:
A. No, no.
CROSBIE, Q.C.:
Q. Okay. You touched on this again today in some of the questioning, but yesterday you made the point that--and none of us doubt it--you see a high volume of this material and a high volume of this test. And so you may be more apt to fairly quickly recognize problems where somebody who's only seeing one or two a month may not.
DR. MULLEN:
A. That's correct.
CROSBIE, Q.C.:
Q. But you may have clarified this and I'm trying to understand, if your material is as unsuitable as you've described, poorly fixed or it suffered in some other way through the process, is that not something an ordinary pathologist or an average pathologist who doesn't see a lot of this, the IHC kind of testing should be able to recognize?
DR. MULLEN:
A. That's correct.

Page 332

CROSBIE, Q.C.:
Q. That would be a skill possessed by any pathologist or that you would expect them to possess.
DR. MULLEN:
A. That's correct.
CROSBIE, Q.C.:
Q. And furthermore, if the pathologist is working with good externals controls, would that help them to spot if there's a difficulty or problem or -
DR. MULLEN:
A. If I recall my testimony, I don't see the external controls--it's not our policy in our laboratory for pathologists to see the external control routinely. If there's a question -
CROSBIE, Q.C.:
Q. That's technologists in your -
DR. MULLEN:
A. Yes, yes.
CROSBIE, Q.C.:
Q. Here, if I understand it correctly, the pathologist was to look at the external controls and they were set out, is that how

Page 333

you understand it?
DR. MULLEN:
A. They were provided to, I don't know the policy in St. John's, but reading--I've forgotten where I read this, that some were not available because they had been sent to the pathologist in the other communities or they did multiple and were sent to the pathologist.
CROSBIE, Q.C.:
Q. Yes, some were sent out, not with controls.
DR. MULLEN:
A. Well, I can't state that.
CROSBIE, Q.C.:
Q. Well, I think we can from what we've seen because we may even have a look at it now in a second. So, pathologists generally should be able to notice the effect of poor fixation?
DR. MULLEN:
A. I would agree.
CROSBIE, Q.C.:
Q. By the way, is this kind of testing, IHC testing, testing where you're looking for antibodies, is this kind of a way of the future? Are we going to see a lot more of this?

Page 334

DR. MULLEN:
A. It's current practice, more, I'm not sure if more. The new trend now is to molecular diagnostics. That's where the research companies and research labs are putting their money because of potential payoffs, but the actual diagnosis, little or--I shouldn't say little--the shift is more to the molecular diagnostics.
CROSBIE, Q.C.:
Q. This is part of a trend towards individualizing treatments more and more to patients?
DR. MULLEN:
A. Yes, genomic medicine.
CROSBIE, Q.C.:
Q. Could be go to Exhibit P-1853, please? Just to explain, sir, this is a document taken out of parallel court proceedings which is the class action that I mentioned just a few minutes ago and these are answers to interrogatories provided by an official of the hospital. Interrogatories are simply written questions and these are written answers. And if we could go to the answer, answer No. 3,

Page 335

please, which -
COMMISSIONER:
Q. Answer No. 3 or page No. 3.
CROSBIE, Q.C.:
Q. Pardon me, Commissioner?
COMMISSIONER:
Q. Was it answer No. 3 or page No. 3?
CROSBIE, Q.C.:
Q. Answer 3, page 2.
COMMISSIONER:
Q. Thank you.
CROSBIE, Q.C.:
Q. I think I have, actually, I got my questions out of order. We should go to question--to answer No. 10, which will be on page 4.
COMMISSIONER:
Q. No. 10?
DR. MULLEN:
A. Do you have the right interrogatory?
CROSBIE, Q.C.:
Q. 1852.
DR. MULLEN:
A. We're on 1853.
COMMISSIONER:
Q. 1852.

Page 336

CROSBIE, Q.C.:
Q. Did I say 1853? 1852, I want to do this in chronological order, so I'm sorry, we should start with 1852 and it's answer 10, page 4. Okay. I think we went through these, actually. Mr. Coffey is just raising whether they're technically entered. I believe we did enter them when Ms. Wegrynowski testified.
COMMISSIONER:
Q. Would you just check our list and make sure these are entered?
CROSBIE, Q.C.:
Q. I remember raising that with you, Commissioner, at the outset.
COMMISSIONER:
Q. There were four exhibits entered, I just don't, off the top of my head, remember what the numbers were.
CROSBIE, Q.C.:
Q. While they're checking that, Doctor, anyway, we should go to No. 10. I believe they were.
COMMISSIONER:
Q. Okay.
CROSBIE, Q.C.:
Q. So the question there, do you have paragraph

Page 337

10?
DR. MULLEN:
A. Yes.
CROSBIE, Q.C.:
Q. Is "What controls were run in all instances?" Answer, "Technical controls were run in all instances. Technical controls are the inclusion of confirmed positive control patient tissue samples." And then "What is the hospital policy on documentation of controls and on retention of the documentation?" Answer, "There is no written hospital or lab policy on the documentation of controls and the retention of such documentation." You can read the rest of the answer, but that's the essential point I wanted to bring out. Then moving down to 13, "Does the documentation show the controls were working in all documented cases?" And answer there is "Not all pathologists referred to the technical and internal controls in their reports. I estimate that in 50 percent of all cases the pathologist referred to the technical controls in his or her report." So can you explain for the Commission, please,

Page 338

what you understand to be going on there?
DR. MULLEN:
A. I just have to look, sorry, before I put my--I want to look at one of my synoptic reports.
CROSBIE, Q.C.:
Q. Specifically what I'm getting at is should this information be reported by the pathologist, the presence of these controls?
DR. MULLEN:
A. Well, the new standards, yes, to be reported, the standard line is put in most reports, positive and negative.
CROSBIE, Q.C.:
Q. New standards as of when?
DR. MULLEN:
A. I can't tell you the exact date.
CROSBIE, Q.C.:
Q. Is it since 2005?
DR. MULLEN:
A. Well, we revised our reports in, I believe in 2005 hen we went to synoptic reporting, so since 2005 we've put it in.
CROSBIE, Q.C.:
Q. Would it be acceptable not to mention or, as it's put here, not to refer to the technical

Page 339

and internal controls in reports even in 2005 or, for that matter, 1997?
DR. MULLEN:
A. Probably '97 it would have been standard practice not to refer, but I -
CROSBIE, Q.C.:
Q. The last answer here is at 17, page 6, please? And the question is, "Please provide a copy of the bench procedure for antigen retrieval during the use of the DAKO system." Answer is, "Please see the bench procedures for certain clones attached." And then can we go to page 7? And, sir, why don't you scroll through at your own pace and you can see what was provided?
DR. MULLEN:
A. Yes. That's the standard hand out.
CROSBIE, Q.C.:
Q. That's the manufacturer's?
DR. MULLEN:
A. Manufacturer's. That's what we--you were asking for the SOP or asking -
CROSBIE, Q.C.:
Q. Bench procedures, how do you understand that?
DR. MULLEN:

Page 340

A. I would provide the standard operating--the SOP, not just that. What we do is this is a reference would be referred to under standard operating procedure. So it's taken -
CROSBIE, Q.C.:
Q. Is this a standard operating procedure?
DR. MULLEN:
A. No, not to my--not in our institution.
CROSBIE, Q.C.:
Q. Could we go then to 1853, please, page 2? This is another interrogatory and answer a little bit later.
DR. MULLEN:
A. Um-hm.
CROSBIE, Q.C.:
Q. And so at page 2, answer 3, we're trying again, "Please attach a copy of the bench manual for the DAKO system, specifically written methodology in antigen retrieval, controls negative and positive, etcetera." Answer, "Please see attached Appendix A." Could you take us there, please? That's page 5. And further on. And again, sir, you may want to scroll through and see what we've been given.

Page 341

DR. MULLEN:
A. I'm not quite sure what all the scratch outs are, but. This would be closer to a SOP. But, I mean, I'd have to go through it point by point by point by point. This sounds--I shouldn't say sounds like, this appears to be something that is specific to the laboratory, and that's basically what a standard operating procedure is. Now, whether it's complete or not, I can't really speak to it. And also it's, this would be something that Ms. Wegrynowski and the technical people would prepare.
CROSBIE, Q.C.:
Q. If you go to page 9, can you do that, sir?
DR. MULLEN:
A. Nine. Okay, one second. Six. And this would be supporting documentation.
CROSBIE, Q.C.:
Q. Does this seem to be DAKO specification literature from the DAKO manufacturer?
DR. MULLEN:
A. Yes, this we would not include as part of our SOP. This would be kept in a manual with reference to the antibody. SOPs are actual

Page 342

procedures. This is supporting documentation.
CROSBIE, Q.C.:
Q. So then when Dr. O'Malley told us a few days ago that we include a statement about our positive and negative lab controls, that's something newer, is it?
DR. MULLEN:
A. Yes. I cannot tell you the specific day that it started, the guidelines. But we instituted it as a standard sort of in the canned message for the synoptic reports in 2005. Before that it may not have been included.
CROSBIE, Q.C.:
Q. P-1604, please? Can you go to page 2, please? We understand these to be handwritten notes of Dr. Cook.
DR. MULLEN:
A. Okay.
CROSBIE, Q.C.:
Q. And reading this note here, he spoke to Dr. Nagihily about why Clarenville discontinued ER and PR slides. Dr. Nagihily replied, "This was due to poor quality and to lack of external controls," plus the fact they were paying for this.

Page 343

DR. MULLEN:
A. And as far as she knows they discontinued without notifying people in St. John's, okay.
CROSBIE, Q.C.:
Q. Is there any contents of that note there that surprises you?
DR. MULLEN:
A. I believe yesterday I answered that one of the first questions was on our, the Mount Sinai Hospital's first contact or first review--not review, first processing of tissue from Clarenville, I had the wrong spot, my apologies, Peninsulas Health Care, if this is--if Clarenville is Peninsulas, we were approached in 1999, the first record I have was October 5th, 1999 that we performed ER and PR staining. In 2005 I had a conversation at the Ontario Association of Pathologists' meeting with Dr. Yassa, who I believe was a pathologist at the time in Clarenville or one of, I don't know if the only or one, and he relayed--I asked him why--this was after I had been approached to do the review, why--he told me he'd been in Newfoundland and he was in

Page 344

Clarenville, so I asked him why he had sent them to us and basically this is the reason, he wasn't provided external quality controls, he was not happy with the service or the quality of the service and therefore he sent them to us. And as I related, from October 5th, '99 until September of 2005, we provided technical services. We cut the--they sent us a block, we cut and stained the slides, each controls and sent them to Newfoundland.
CROSBIE, Q.C.:
Q. So what you understood from other sources corroborates what's in that?
DR. MULLEN:
A. Yes, yes.
CROSBIE, Q.C.:
Q. Okay. Sir, perhaps you could assume that this is accurate information. Up to around 1999 here we had an enzyme immune assay technique performed in the biochemistry division of the lab at Eastern Health and the Health Sciences, and then testing for IHC was switched to the anatomical pathology division. Anatomical pathology is used to doing ordinary histology, right?

Page 345

DR. MULLEN:
A. Plus electron microscopy, immunohistochemistry, the whole cytopathology, the whole area.
CROSBIE, Q.C.:
Q. What would you do if you were in charge of the transition, as I just described it, to ensure good reliable IHC staining?
DR. MULLEN:
A. Basically I would establish the--I would optimize the antibodies. I would--looking at the biochemistry and basically I believe what probably Dr. O'Malley and Ms. Wegrynowski, we established tissue a tissue microray. We would go back to tissue, archival tissue, well fixed, well preserved, that was called positive, low positive, and I can't give you the actual thinamoles (phonetic), positive, low positive and negative and establish our antibody that would be--that would do the optimization to that. Then we would, once we've done that, then I'd run a concordance survey to see if we would go back to archival cases and look at stain and see what the positivity rate was compared to the Ligand

Page 346

binding assay or whatever the assay was at the time. That's basically -
CROSBIE, Q.C.:
Q. How large a number of cases would be included in a concordance if you were doing this transition?
DR. MULLEN:
A. Depends on the statistical results. You do enough to be statically robust, so I can't give you an--20, 40, 50, somewhere in that rage.
CROSBIE, Q.C.:
Q. Depending on what results you're getting?
DR. MULLEN:
A. Yes, if they weren't--you would keep--then you'd start over again. I mean, you'd have to--it'd be iteration, if it wasn't working, you would optimize again.
CROSBIE, Q.C.:
Q. Would you have to ask yourself some questions about training for staff who were going to be doing the procedure?
DR. MULLEN:
A. Certainly. I mean, that's all part of the validation of an antibody or introduction of

Page 347

an antibody.
CROSBIE, Q.C.:
Q. Okay. So you understand that to include training of staff?
DR. MULLEN:
A. Yes.
DR. MULLEN:
A. That's the way, okay, that's the way your mind works, okay.
DR. MULLEN:
A. Yeah, sorry.
CROSBIE, Q.C.:
Q. So personnel issues would have to be looked at and, I suppose, a budget would have to be drawn up for this, would it?
DR. MULLEN:
A. Well, we would hope there would be a transfer of the budget from biochemistry to pathology because stopping one test in one area, personnel, the personnel and reagent support, etcetera, would be hopefully transferred to pathology.
CROSBIE, Q.C.:
Q. You would expect this to be no extra cost?
DR. MULLEN:

Page 348

A. I don't know what the Ligand binding assay cost.
CROSBIE, Q.C.:
Q. Okay. Can we bring up document 1850, please? This is a memorandum from Dr. Khalifa.
DR. MULLEN:
A. Yes.
CROSBIE, Q.C.:
Q. And it's addressed to all Newfoundland pathologists, February, 1998. It's about reporting of estrogen and progesterone receptor immunohistochemical results. I'm just going to give you an opportunity to scan through that, it's a few pages in length. On page 3 you'll notice "Positivity is defined by nuclear staining detected in any number of malignant cells," and it goes on to discuss the 30 percent -
DR. MULLEN:
A. The 30 percent, the cut off, the American (unintelligible) Surgical Pathology, yes.
CROSBIE, Q.C.:
Q. Which is a 1990 publication?
DR. MULLEN:
A. Yes, that's correct.

Page 349

CROSBIE, Q.C.:
Q. And it's repeated down below in example 2 in that table there.
DR. MULLEN:
A. All right.
CROSBIE, Q.C.:
Q. And then you'll see a report of our experience over a nine-month period. January '97 to September, '97.
DR. MULLEN:
A. Um-hm.
CROSBIE, Q.C.:
Q. I take it this is the confirmation exercise?
DR. MULLEN:
A. Yes, yes. Okay.
CROSBIE, Q.C.:
Q. And you see from the tables on the page you're on and also the comments that this was performed on a total of 19 cases for estrogen and 17 cases for progesterone?
DR. MULLEN:
A. Okay.
CROSBIE, Q.C.:
Q. Is that a small series for doing this kind of exercise?

Page 350

DR. MULLEN:
A. Were the results statistically significant?
CROSBIE, Q.C.:
Q. You're the expert.
DR. MULLEN:
A. I can't do the stats, I can't do the chi square off the top of my head, but -
CROSBIE, Q.C.:
Q. So why don't you explain what would have to be performed to know that, to answer the question you just asked me?
DR. MULLEN:
A. Basically you'd have to do statistics, are these--is there a significant difference, and if they are, fine, if they're not, fine.
CROSBIE, Q.C.:
Q. Okay. Do you see that analysis in the paper?
DR. MULLEN:
A. No, no.
CROSBIE, Q.C.:
Q. Is it likely -
DR. MULLEN:
A. I really would, I mean, to comment on this I'd really have to sit down and go through and review it. I mean, reading a six-page

Page 351

document at quarter to five after two days, I'd have to--really going beyond what I feel comfortable doing until I actually review it.
CROSBIE, Q.C.:
Q. I'm sure we can sympathize with you. So -
DR. MULLEN:
A. And I think -
CROSBIE, Q.C.:
Q. - thanks for helping us to that extent.
DR. MULLEN:
A. But I think the statistician who is going to review the results might be a better person to ask.
CROSBIE, Q.C.:
Q. Just quickly, can we go to 0067, which is a letter from Dr. Cook to Dr. Robert Williams, the Vice President Medical Services. And page 2 of that, please?
DR. MULLEN:
A. May 24th, okay.
CROSBIE, Q.C.:
Q. At the foot of that page 2 it's, Dr. Cook is explaining to Dr. Williams what Dr. Ejeckam did at the foot. Here we are. He says, "In early 2003 Dr. Ejeckam, our point man,

Page 352

discontinued testing of the ER/PR receptors with the manual method for a six-week period. A memo was circulated to all pathologists across the province stating this. The technique was temporarily halted because of erratic staining which required readjustments of titration and staining times." So that's essentially what Dr. Ejeckam adjusted or tinkered with is the staining times and titration.
DR. MULLEN:
A. Um-hm.
CROSBIE, Q.C.:
Q. "Once he felt confident of the reliability of staining the test was reintroduced."
DR. MULLEN:
A. Okay.
CROSBIE, Q.C.:
Q. And now, sir, I'd like to take you to a table which I guess we may have to enter, which I think we all have a copy of. That's called P-1841.
MR. SIMMONS:
Q. Excuse me, Commissioner, I know it's twice in one afternoon, but this is the document we

Page 353

were just given on break and haven't had an opportunity to look at it beforehand, but it appears to be a collection of statistics and data for--compiled and prepared for Mr. Crosbie by Dr. Charles Hutton. And it doesn't have the appearance of being anything that Dr. Mullen has been involved in preparing or even with--before as far as I know, so I just wonder if this is a document which we should be being put in thorough this witness or if it should wait until when Dr. Hutton is called.

COMMISSIONER:

Q. Mr. Browne, you're on your feet, as well.

MR. BROWNE:

Q. Similarly, Commissioner, we've heard about reliability and producibility and I have some concerns about what's gone into this without having the witness who's prepared it under oath and examined, (inaudible) no reliability and this kind of thing.

COMMISSIONER:

Q. Well, let's find out what the comfort of the witness is with what he's had -

CROSBIE, Q.C.:

Q. Perhaps I could address that? The information

Page 354

-

COMMISSIONER:

Q. Yes, why don't you do that.

CROSBIE, Q.C.:

Q. - in the tables is taken directly out of the answers to interrogatories. In other words, it comes straight from Eastern Health. That's the information contained in, under "Total Tests" in that column there, as noted by footnote 2. And also in "Total Negatives", in that column there. And "False Negatives", in that column there is also taken from information supplied by Eastern Health. If we want to walk back to the answers, I can prove that, you know, step by step, I've done that for myself, or anyone can check that. The rest of these percentages are merely arithmetic calculations anyone can do by use of a calculator. It would be unfortunate if I couldn't ask this gentleman about his comments on these results.

COMMISSIONER:

Q. Well, let's first find out if--are you aware that these are materials coming from your client?

Page 355

MR. SIMMONS:

Q. I can only read the bottom that references these two exhibits, but I haven't had a chance to cross reference or to see if, in fact, the numbers here are taken directly out of those answers to interrogatories or if these calculated percentages are correct or if they're taken from the interrogatories at all. I mean, again, I wonder at the utility of -

COMMISSIONER:

Q. Just a minute now, Mr. Simmons. In the event that--what would be your position in the event that Mr. Crosbie's statement is absolutely correct and that is that they came out of interrogatories produced by Eastern Health in another proceeding and there were mathematical calculations for the purpose of which this question, you can assume, were correct?

MR. SIMMONS:

Q. I still question what point and purpose is of putting this to Dr. Mullen and inviting his comment on.

COMMISSIONER:

Q. Mr. Browne, do you want to add in?

MR. BROWNE:

Page 356

Q. Again, if I can go back to reliability and reproducibility and Dr. Mullen previous comment about statistical analysis. I mean, there are numbers here, percentages which I'm reading that Dr. Hutton has tabulated and we don't know how--whether he's gotten that corrected--correct or not and we can't examine him on it and that's the -

COMMISSIONER:

Q. At the moment. That doesn't mean you can't in the future.

MR. BROWNE:

Q. True, but I guess the question being, I mean, can this witness comment on it.

COMMISSIONER:

Q. All right, thank you. Now, Mr. Crosbie, I take the point, but I do think we do have to resolve, and I'll leave it to you, ask the question of the witness of whether or not he's in a position to answer, he feels comfortable with answering questions related to these documents. For myself, if the witness is comfortable with them and if it can--we can deal with this as an exhibit taken in on the basis of the, noting the objections of these

Page 357

two parties with a view that confirmation of the information may have to be checked in the future.

CROSBIE, Q.C.:

Q. Sure.

COMMISSIONER:

Q. If this witness is comfortable with answering questions related to that kind of material.

CROSBIE, Q.C.:

Q. It's not hard to confirm the information, just by going back to the answers. But at this late point on Friday afternoon maybe we can skip that step -

COMMISSIONER:

Q. Well, yes, I'm sorry, Mr. Clements?

MR. CLEMENTS:

Q. Commissioner, I wonder if I could provide my client some advice on -

COMMISSIONER:

Q. You can, indeed.

MR. CLEMENTS:

Q. - how he might answer the questions and could we have a recess for one or two minutes for me to do that?

COMMISSIONER:

Page 358

Q. Yes. Mr. Crosbie, would you--you realize that this is a witness from out of town, so whatever way we have to deal with this, we have to deal with it today.

CROSBIE, Q.C.:

Q. Yes, indeed.

DR. MULLEN:

A. I have an 8:00 flight, so, that's fine, it's not that far to go.

COMMISSIONER:

Q. Mr. -

COFFEY, Q.C.:

Q. If we could, Commissioner, it might facilitate things, too, certainly from Mr. Clement's perspective, if a question could just be phrased without being answered, at least we'd have some sense about -

COMMISSIONER:

Q. Of what the question is to be.

DR. MULLEN:

A. What you're asking me.

COMMISSIONER:

Q. Yes. Thank you, Mr. -

CROSBIE, Q.C.:

Q. Well, one question I would ask is assuming

Page 359

these figures to be accurate, or the table to be accurate, you can see there at a certain point in time the premise is that Dr. Ejeckam did an intervention and the rest of us have heard a lot of information about that. His intervention appeared to result in getting the positivity rates up, but if you look in the column under "False Negatives", the false negative rate appeared to remain high, if not go higher. And one question I wish to ask the witness was could he venture any explanation as to how that could be?

COMMISSIONER:

Q. All right. Well, why don't we take that five-minute break that's been asked for and you can consult with your client.

(RECESS)

COMMISSIONER:

Q. Please be seated. Mr. Clements?

MR. CLEMENTS:

Q. Yes. Mr. Crosbie can ask his question. I don't know that the witness is going to be able to help him with the answer, but the witness can explain that.

COMMISSIONER:

Page 360

Q. Oh, okay. Gets a little more complicated.

CROSBIE, Q.C.:

Q. I really didn't expect it to be simple.

COMMISSIONER:

Q. Okay. Now, are we all clear? What I'm allowing here is the asking of the question and we'll leave it to the witness to determine whether or not he feels that he's in a position to provide an answer given the circumstances and he will explain what those are. What use I may make of this you may argue in the future based on whether or not the underlying facts are or are not established. Now, do you want to put your question again, Mr. Crosbie, so we all know what it is?

CROSBIE, Q.C.:

Q. Yes, I believe my -

THE COMMISSIONER:

Q. Oh, and before you do that, I know--because the document itself, what was the number again? Could you give it to me?

CROSBIE, Q.C.:

Q. P-1841.

THE COMMISSIONER:

Page 361

Q. P-1841 and that has not been put into evidence, as I understand it.
REGISTRAR:
Q. No, Commissioner.
THE COMMISSIONER:
Q. Okay. We'll make it an exhibit.
EXHIBIT ENTERED AND MARKED P-1841.
CROSBIE, Q.C.:
Q. Thank you.
THE COMMISSIONER:
Q. Now, would you put your question please.
CROSBIE, Q.C.:
Q. Yes, I believe the question was you can see there are various percentages by year, which is I mentioned before, derived from data provided in sworn answers to interrogatories that we quickly looked at as we were passing along there about a half an hour ago. So the percentages give you false negative rates in the column on the right-hand side, and you can also see positivity rates in the column in the third from the left.
DR. MULLEN:
A. Uh-hm.
CROSBIE, Q.C.:

Page 362

Q. And what I was going to ask you was with an improvement in the positivity rate for 2003 to the level of 76 percent, which I believe you, from information you gave us before would be an acceptable range, what you'd be looking for, yes?
DR. MULLEN:
A. That is correct.
CROSBIE, Q.C.:
Q. That's an improvement from the overall positivity rate of 58 percent in the period 1997 to 2002, yes?
DR. MULLEN:
A. Yes, correct.
CROSBIE, Q.C.:
Q. Appears to follow the intervention by Dr. Ejeckam, as far as you can tell, yes?
DR. MULLEN:
A. Yes, that's correct.
CROSBIE, Q.C.:
Q. So it is, intervention seems to have a positive effect on the quality of the process to the extent that it raised the positivity rate.
MR. CLEMENTS:

Page 363

Q. Excuse me, that's not the question that Mr. Crosbie previously put. He's now cross-examining the witness on -
CROSBIE, Q.C.:
Q. Well, I'm just bringing him, I'm just bringing everyone through it step by step. These are all factual things in it and my next question, if he agrees with that is can he explain why the overall false negativity rate or for that matter for 2003 remains stuck at 44 percent and over the entire period, 45 percent, that's the question.
THE COMMISSIONER:
Q. Is the witness in a position to assist?
DR. MULLEN:
A. I can't speak to this data and I don't feel comfortable speaking to it, but I think what's been explained both by Ms. Wegrynowski and myself and other witnesses, there are approximately 30, 40 steps that any one of those could account for the abnormalities, beyond that, I can't be more specific. I'm sorry, but I just can't analyze the data.
CROSBIE, Q.C.:
Q. Let me ask one more question.

Page 364

THE COMMISSIONER:
Q. Well, let's find out what the question is and then we'll determine whether or not any doesn't object to -
CROSBIE, Q.C.:
Q. I want to know what the witness thinks or how he evaluates if it's true, a false negative rate of 45 percent?
THE COMMISSIONER:
Q. That's an abstract question as to what he-- what his reaction is to a false negative rate of 44 percent?
CROSBIE, Q.C.:
Q. If that's an accurate number.
THE COMMISSIONER:
Q. If that is an accurate number.
DR. MULLEN:
A. And it doesn't appear on here, so it's not a specific column, so that would be a very high false negative rate.
CROSBIE, Q.C.:
Q. I'm sorry, it is there, under false negative grand total.
DR. MULLEN:
A. Oh grand total, my apologies.

Page 365

THE COMMISSIONER:
Q. Date, 2003 on the -
DR. MULLEN:
A. I was looking at any of the specifics, you're adding year by year by year.
CROSBIE, Q.C.:
Q. Grand total for the period.
DR. MULLEN:
A. It would be a high rate.
MR. SIMMONS:
Q. Commissioner, if I might on that point, it depends too on what's intended by the term "false negative rates" and what that's a percentage of.
DR. MULLEN:
A. Yes, I mean, -
THE COMMISSIONER:
Q. Which goes back to the witness's earlier point in terms of knowledge of that underlying -
DR. MULLEN:
A. I don't know what this is, so 45 would be high if--it's best not to go speak to the specifics in this case.
CROSBIE, Q.C.:
Q. Thank you.

Page 366

THE COMMISSIONER:
Q. Thank you, Mr. Crosbie. Mr. Pike?
MR. PIKE:
DR. BRENDAN MULLEN, EXAMINATION BY MR. MARK PIKE
MR. PIKE:
Q. Dr. Mullen, Mark Pike is my name. I'm the lawyer for the Newfoundland and Labrador Medical Association. Just a small point and maybe I missed it earlier, when you carried out this review for the Commission of some slides that were sent to you -
DR. MULLEN:
A. Are you referring to the data I spoke to this morning?
THE COMMISSIONER:
Q. The data sent by the--the slides sent by the Commission?
MR. PIKE:
Q. Yes, yes, I am.
DR. MULLEN:
A. So that's exhibit -
THE COMMISSIONER:
Q. Are we looking at P-1837?
MR. PIKE:
Q. Yes, P-1837. Just, I'm wondering whether you

Page 367

are aware of the criteria that was used to determine which slides you'd be reviewing, whether you participated in the selection criteria of those slides or whether you just reviewed what you were given?
DR. MULLEN:
A. I was reviewing what I was given. I have subsequently become aware of what the criteria were, but I didn't know the criteria until last night.
MR. PIKE:
Q. Okay, that's my question. Thank you very much.
THE COMMISSIONER:
Q. All right, Mr. Clements, did you have any questions today?
MR. CLEMENTS:
Q. Just one.
DR. BRENDAN MULLEN, EXAMINATION BY MR. SIMON CLEMENTS
MR. CLEMENTS:
Q. Dr. Mullen, is there any information that you would like to give to the Commissioner on the training of pathologists, regarding IHC procedures and your comments generally on that topic?

Page 368

DR. MULLEN:
A. This will be, I wanted an opportunity to speak on one of my major concerns, I mean, I think Ms. Wegrynowski spoke about her concerns about having adequately training medical technologists. I want to mirror that for the training of pathologists. At the moment pathologists are focused on, I should say pathology training programs are focused on the cutting edge, the molecular diagnostics. We've lost track of, as we can see from this material, the necessity to be able to analyze routine material and to do any of the special stains that include in immunohistochemistry. So if one of the recommendations or I don't want to prejudge what you're going to say, is that the training programs be very sensitive to the requirements for basic training, that the diagnosis, the processing of tissue, the interpretation of tissue be enhances, not at the expense of the cutting edge, but be preserved and enhanced, that's basically -
THE COMMISSIONER:
Q. So the point being that in our rush to the latest in technology, we should not forget

Page 369

that there are basics there that everybody should know.

DR. MULLEN:

A. Yes, that's correct. You have to walk before you can run.

THE COMMISSIONER:

Q. Thank you.

DR. MULLEN:

A. That was all, thank you.

THE COMMISSIONER:

Q. Was there anything arising, Mr. Coffey?

DR. BRENDAN MULLEN, EXAMINATION BY BERNARD COFFEY, Q.C.

COFFEY, Q.C.:

Q. Yes, just one or two, Commissioner, if I could? Just Doctor, something that Mr. Simmons raised with you. I think he pointed-- if we could, please, Registrar, Exhibit P-1811? And go to page three, please? I believe, if we could -

DR. MULLEN:

A. Which one was it?

COFFEY, Q.C.:

Q. There was here, down--I believe Mr. Simmons referred you to the -

DR. MULLEN:

Page 370

A. 7788

COFFEY, Q.C.:

Q. Yes, 99SU7788, it was a block 1B and a block 1C from that specimen, and he referred you to the fact that in the block 1B, your analysis, as reported in the retrospective review was less than one for ER and zero for PR, and then on block 1C, which is a different block, the slides from that you reported as two for ER and zero for PR.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. That sort of--well, the zero for the PR are identical.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. The difference between one block reporting at less than one and a block, that's block 1B, and block 1C reporting at two, is that sort of a difference, bearing in mind that, I take it, the two different blocks are two different pieces of tissue?

DR. MULLEN:

Page 371

A. That is correct.

COFFEY, Q.C.:

Q. Is that expected or reasonable in the circumstances, do you believe?

DR. MULLEN:

A. Yes, yes. The implication here in our situation that one would trigger therapy, the other one wouldn't. That's -

COFFEY, Q.C.:

Q. Yes.

DR. MULLEN:

A. But, you know, the difference between a one and a two is--you know, there's a 50 percent difference, but it's -

COFFEY, Q.C.:

Q. It's one in 100 as opposed to two in 100?

DR. MULLEN:

A. Yes. Yes, you have to remember that.

COFFEY, Q.C.:

Q. And if we could, please, again something that Mr. Simmons asked you about a particular instance, Exhibit, Registrar, P-1837, page one? This is the April 2008 spreadsheet.

DR. MULLEN:

A. Yes, okay.

Page 372

COFFEY, Q.C.:

Q. And Mr. Simmons, in fact, he referred you, I believe, to ID No.--the first row, ID No. 6. As it turns out, the specimen number is 97SU6297. It's block A and as we come across here, he indicated to you, of course, that you--had you indicate that well, looking at the original Newfoundland report, Newfoundland and Labrador original pathology report, and if you could, and you have here, looking at the piece of paper you've reported here that you interpreted and recorded it with the ER was their reported as negative and PR as 90.

DR. MULLEN:

A. Yes.

COFFEY, Q.C.:

Q. And that he had you indicate though that N in this context, you wouldn't know the cut off was one, 10 or 30?

DR. MULLEN:

A. That's correct.

COFFEY, Q.C.:

Q. And therefore it could be variable and therefore, in calling it as Mount Sinai Hospital discordant, it -

Page 373

DR. MULLEN:
A. I may have taken liberties because my value is zero.
COFFEY, Q.C.:
Q. Yes.
DR. MULLEN:
A. So I would have -
COFFEY, Q.C.:
Q. That would be zero in the context of, I take it, your looking at an original Newfoundland slide?
DR. MULLEN:
A. Yes, this is the original of Newfoundland, so the negative -
COFFEY, Q.C.:
Q. And just to put this in context, if we could bring up, please, Exhibit P-1811, page 14, please, and I'm looking at that, if we could, just a moment please, Commissioner, if I could, and bearing in mind or recalling that the specimen number was 97SU6297.
DR. MULLEN:
A. Yes, okay, there it is.
COFFEY, Q.C.:
Q. And if we go down toward the bottom exactly

Page 374

there, Doctor, toward the bottom of the page, it's about the 1-2 -
DR. MULLEN:
A. 80/90.
COFFEY, Q.C.:
Q. - eighth from the bottom.
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. And we come across there, it's block A and in January or before that, but certainly by January of 2006, on block A, the slides prepared at Mount Sinai, you had reported the ER as 80 and the PR as 90?
DR. MULLEN:
A. That's correct.
COFFEY, Q.C.:
Q. So I gather that in terms of the issue of concordance or discordance, in fact -
DR. MULLEN:
A. Whether it was 30 -
COFFEY, Q.C.:
Q. The slide, the PR slide that you produced at Mount Sinai, you called as 90?
DR. MULLEN:

Page 375

A. Yes.
COFFEY, Q.C.:
Q. And apparently, and looking at the original report from the pathology, who's unspecified, the report that was sent to you, and you looked at, you recorded or noted that that pathologist, back in apparently 1997, had recorded the PR as 90 as well?
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. But the pathologist back in '97 had recorded the ER as negative, N negative, whatever that might be.
DR. MULLEN:
A. Yes.
COFFEY, Q.C.:
Q. However, you had -
DR. MULLEN:
A. Zero.
COFFEY, Q.C.:
Q. You had zero for what you saw -
DR. MULLEN:
A. On the original slide.
COFFEY, Q.C.:

Page 376

Q. And therefore perhaps agreeing with what he was seeing there, but on the--but when on a retrospective slide, the one from Mount Sinai, the one processed at Mount Sinai, you had recorded it or reported it, the ER has 80?
DR. MULLEN:
A. That's correct.
COFFEY, Q.C.:
Q. And there would be, I take it, under any--would there be any circumstances under which 80 and negative would not be discordant?
DR. MULLEN:
A. No, if I remember correctly, the cut off in '97, I don't know when you changed to ten, it was 30. Then it subsequently went to ten, and I'm not sure, through my analysis or through my data when it was called--when it changed to ten.
COFFEY, Q.C.:
Q. But even from 30 to 80, I take it, that would be discordant?
DR. MULLEN:
A. Yes, it would be discordant, yes.
COFFEY, Q.C.:
Q. Just wanted to--and again, they're the

Page 377

questions I have, Commissioner. I do want to thank you, Doctor.

THE COMMISSIONER:

Q. All right, thank you very much.

DR. MULLEN:

A. You're welcome.

THE COMMISSIONER:

Q. Thank you all. This comes--marks the end of a long week, and I'm sure for you, Dr. Mullen, I want to thank you very much for having come all this way, you and the many others from Mount Sinai who've helped us during this week. We are most grateful to you and wish you a safe journey home.

DR. MULLEN:

A. Thank you.

THE COMMISSIONER:

Q. Thank you, Mr. Clements, for your contribution as well, and we wish you, as well, a safe journey back. As far as I know, this is our last witness from Mount Sinai, so we're not likely to see Mr. Clements again in this process. Perhaps in another forum, Mr. Clements.

COFFEY, Q.C.:

Page 378

Q. Well, I won't commit to that, but right now, it's not anticipated, but I'm not giving any commitment.

THE COMMISSIONER:

Q. All right.

DR. MULLEN:

A. I would prefer a commitment on the record.

COFFEY, Q.C.:

Q. Thank you, Doctor.

THE COMMISSIONER:

Q. Which I don't blame you.

COFFEY, Q.C.:

Q. You won't be back though.

DR. MULLEN:

A. Thank you.

THE COMMISSIONER:

Q. I remind everybody that we will begin sittings next week on Wednesday, so you can enjoy that holiday that you lost this week on Monday of this week. Yes, next week, sorry. The holiday that you lost on Monday, you'll get on this Monday, and we'll see you all on Wednesday at 9:30.

COFFEY, Q.C.:

Q. Thank you, Commissioner.

Page 379

THE COMMISSIONER:

Q. Thank you.

Upon conclusion.

Page 380

CERTIFICATE

I, Judy Moss, hereby certify that the foregoing is a true and correct transcript in the matter of the Commission of Inquiry on Hormone Receptor Testing, heard on the 27th day of June, A.D., 2008 before the Honourable Justice Margaret A. Cameron, Commissioner, at the Commission of Inquiry, St. John's, Newfoundland and Labrador and was transcribed by me to the best of my ability by means of a sound apparatus.

Dated at St. John's, Newfoundland and Labrador this 27th day of June, A.D., 2008

Judy Moss

-H-

-I-

-J-

-K-

-L-

-U-