COMMISSION OF INQUIRY
ON HORMONE RECEPTOR TESTING

BEFORE THE HONOURABLE JUSTICE CAMERON - COMMISSIONER

October 10, 2008

Appearances:

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

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

Peter Browne, Q.C./Jane Hennebury . . . Doctors Kara Laing et al

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

Darlene Russell.. . . . . Members of the Breast Cancer
. . . . . Testing Class Action

Mark Pike, Q.C. . . . . NL Medical Association
Jennifer Newbury . . . . . Canadian Cancer Society (NL Division)
Blair Pritchett. . . . . Central, Western and Labrador-Grenfell
Regional Integrated Health Authorities

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Certificate

THE COMMISSIONER:

Q. Please be seated. Mr. Coffey.

COFFEY, Q.C.:

Q. Thank you, Commissioner. We have two witnesses today actually and they're going to testify simultaneously. They're Bryan Hewlett and William Parks.

MR. BRYAN HEWLETT (SWORN) EXAMINATION BY BERNARD COFFEY, Q.C.

REGISTRAR:

Q. Would you please state and spell your complete name for the Commission?

MR. HEWLETT:

A. Bryan Hewlett, B-R-Y-A-N H-E-W-L-E-T-T

MR. WILLIAM PARKS (SWORN) EXAMINATION BY BERNARD COFFEY, Q.C.

REGISTRAR:

Q. Thank you. Would you please state and spell your complete name for the Commission?

MR. PARKS:

A. William Parks, W-I-L-L-I-A-M P-A-R-K-S.

COFFEY, Q.C.:

Q. Thank you, gentlemen. Have a seat. Commissioner, there are several, well, slightly more than several more exhibits I'm

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going to ask be entered, please. They are Exhibits P-3356, 3357, 3358, 3359, 3366, 3367 and 3368.

THE COMMISSIONER:

Q. Entered.

EXHIBITS ENTERED AND MARKED P-3356 THROUGH P- 3359 INCLUSIVE

EXHIBITS ENTERED AND MARKED P-3366 THROUGH P- 3368 INCLUSIVE

COFFEY, Q.C.:

Q. Thank you, Commissioner. Registrar, would you bring up, please, Exhibit P-3356? And there, gentlemen, on the screen in front of you, you'll see a curriculum vitae for Bryan Hewlett. Mr. Hewlett, is that your curriculum vitae?

MR. HEWLETT:

A. It is.

COFFEY, Q.C.:

Q. And while I'm at it, I'll address the other exhibit. If I could have Exhibit P-3357, please? Mr. Parks, is this your curriculum vitae?

MR. PARKS:

A. Yes, it is.

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COFFEY, Q.C.:

Q. Now I'm going to ask you, starting with yourself, Mr. Hewlett, perhaps you could give the Commissioner an overview of your educational and professional background, Mr. Hewlett, please?

MR. HEWLETT:

A. I took my initial training as a medical technologist in Nottingham, England. Back in those days, it was an apprenticeship type program. So one was hired as a student and then given day release and evening classes. It was a three-year course for general medical technology. When I completed that, I then did an additional two years with a specialty in histotechnology, all while I was working for a pharmaceutical research company. In 1962, I immigrated to Canada and went to Thunder Bay, Ontario. In 1964, I obtained my Canadian registration as a medical technologist, and in 1966, obtained an advanced registration with the CSMLA.

I worked in North Western Ontario until 1992 as a supervisory technologist in histotechnology, developing all sorts of

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techniques, including immunohistochemistry, which I was actually first exposed to back in the '50s in England. I also was an instructor for the med-lab tech program in Thunder Bay, and in the '80s, we started a university program, an honours degree course at Lakehead University, and I was a sessional lecturer for that. 1992, I moved to McMaster as a research associate, opened up a core research histology facility and subsequently became the technical specialist for McMaster University Medical Hospital in anatomic pathology, and then on restructuring, was appointed as the technical specialist in immunohistochemistry and molecular pathology for the Hamilton Regional Laboratory Medicine Program, where I remained until I retired in 2002. Since then, I have been a consultant for the Quality Management Program, Laboratory Services of Ontario.

COFFEY, Q.C.:

Q. And if I could, please, Mr. Hewlett, I'm just going to--there's a couple of things in your CV. Page ten, you've noted here, of your CV, there's recent publications, books, "Optimizing IHC Technique, a Laboratory

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Handbook."

MR. HEWLETT:

A. Um-hm.

COFFEY, Q.C.:

Q. Published in 2001.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. So you have published a text on optimizing IHC techniques, by way of providing or producing a laboratory handbook, and then beginning on that page, there are a number of journal articles that continue on, in fact, for pages, and then abstracts and posters as well that you've been involved in presentations over the years.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. I'm going to return, if I could, to page one of your curriculum vitae because under teaching and continuing professional development, you have written "teaching students, fellow technologists and laboratory scientists the theory and practice of both

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microscopy and histotechnology has always been an integral part of my 47-year professional career and is of paramount importance to me," and you've noted "although I decreased my formal teaching commitments to students in recent years, I was previously heavily involved in teaching at both the entry and advanced levels" and that would be teaching histotechnologists?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And particularly immunohistochemistry?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. Mr. Hewlett, in terms of your more recent involvement, I understand that you've been involved in an ad hoc committee recently that met in the United States?

MR. HEWLETT:

A. That's correct.

COFFEY, Q.C.:

Q. Could you tell the Commissioner what that was about, just to give her some sense of, having

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read your CV, of what your current--the nature of your current involvement is?

MR. HEWLETT:

A. It was a one-week immunohistochemistry workshop in Santa Barbara at the end of January and I was on the program as a speaker, and I was approached to go down early to take part in a meeting regarding recommendations for the testing for estrogen receptors. That was the ad hoc committee for immunohistochemistry.

COFFEY, Q.C.:

Q. Is David Dabbs involved in that committee?

MR. HEWLETT:

A. Yes, he is.

COFFEY, Q.C.:

Q. This is this ad hoc committee that he and a number of other pathologists and technologists are involved in?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And in terms of that ad hoc committee, do you have any understanding about kind of the current report or paper that they are

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producing?

MR. HEWLETT:

A. It has been accepted for publication. I understand it will be published in December in the Journal of Applied Immunohistochemistry and Molecular Morphology.

COFFEY, Q.C.:

Q. And -

THE COMMISSIONER:

Q. That's a catchy title.

MR. HEWLETT:

A. Yes, isn't it.

COFFEY, Q.C.:

Q. That's December of this year, I take it, you understand?

MR. HEWLETT:

A. That apparently is the target, yes.

COFFEY, Q.C.:

Q. And Dr. Dabbs has testified here about his own involvement in it. So you were involved with that, the group that he was involved with, and I take it you're involved with many other organizations and groups?

MR. HEWLETT:

A. Yes, I couldn't attend the first meeting of

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that group, which was in Florida the year before, because I had another commitment, but I did attend the latest one.

COFFEY, Q.C.:

Q. Mr. Hewlett, as well, I take it that as recently as the last month, you attended at conference in the United States?

MR. HEWLETT:

A. That's correct.

COFFEY, Q.C.:

Q. And where was that?

MR. HEWLETT:

A. That was in, oh dear, Pittsburgh.

COFFEY, Q.C.:

Q. And that was a conference of what, what type of a -

MR. HEWLETT:

A. That was the National Society for Histotechnology, their annual conference, and I was giving a workshop there.

COFFEY, Q.C.:

Q. Mr. Parks, could you please give the Commissioner an overview of your educational and professional background?

MR. PARKS:

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A. Okay. I did -
COFFEY, Q.C.:
Q. I appreciate you're a lot younger than Mr. Hewlett.
MR. PARKS:
A. Yes, I have 20 years less experience. I went through the program in the early '80s at Algonquin in Ottawa. It's a community college, and it's a three-year program and I spent a year in the hospitals in all the different laboratories, an entire year of rotating through all the laboratories. After I graduated, I worked in a variety of the labs until I found the one I liked, which took me a year, and then I got into histology, and I was lucky. I got into histology at the time that the pathologists were starting to come back from fellowships in the States and they were bringing back immunohisto techniques and I was lucky enough to be involved at the ground floor of setting up histology or immunohistochemistry in Ottawa at the Civic Hospital, at that time, and I have been involved in it ever since.
I've been practising as a bench tech, I

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worked on the bench yesterday even, for the last 26 years now, and I've been--I do a lot of the teaching of my new staff. I believe in a very structured training of staff when they come in, so that there is consistency in the lab. So I'm very involved in the training of all my new staff. I am involved in, you know, in implementation of new technologies and I have kept my education up. I did a Bachelor's degree in Business Administration as a different approach to the hospital, as opposed to advance in my science. So I have a combination of education.
COFFEY, Q.C.:
Q. What's your current position?
MR. PARKS:
A. I am the charge technologist of the histology lab at the Ottawa Hospital. It's now a--the whole Ottawa region has been consolidated into one major histology lab. So it's quite a large laboratory in one site.
COFFEY, Q.C.:
Q. And the population base that that serves is about what?
MR. PARKS:

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A. Eastern Ontario. It's probably one and a half million, I think is probably the -
COFFEY, Q.C.:
Q. The catchment area as it were?
MR. PARKS:
A. Yeah, about that size.
COFFEY, Q.C.:
Q. Now I understand that--well, perhaps, Mr. Hewlett, you could tell the Commissioner then about--I understand that both of you gentlemen recently, this past month, in September of 2008, had occasion to visit St. John's to conduct a review here in St. John's. Mr. Hewlett, perhaps you could tell the Commissioner about how that came about? I believe you had a conversation with myself, and how it came about and what it was you understood it was you were being asked to do here, and the approach, your tasking of Mr. Parks with this and how it unfolded, just in terms of outlining how you ended up here.
MR. HEWLETT:
A. Well, I was approached by you, Mr. Coffey, on behalf of the Commission, to have a look at the front end of the laboratory, that is

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everything from specimen receipt through fixation, processing, right up to the preparation of the sections prior to staining. It's an integrated process, not a series of small steps, as it's often represented, and so that was basically the point.
COFFEY, Q.C.:
Q. Okay.
MR. HEWLETT:
A. To have a look to see what was actually happening and to compare that to the procedure manuals which state what is supposed to be happening.
COFFEY, Q.C.:
Q. Now Mr. Hewlett, Mr. Parks was identified. I believe you were -
MR. HEWLETT:
A. Yes, you asked if I knew of anybody else who did this sort of thing, and I mentioned a couple of people. Mr. Parks being one of them, and so we came down together to do this. We worked independently. So I went to one location and Mr. Parks went to the other and then we traded places over subsequent days.
COFFEY, Q.C.:

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Q. Now Mr. Parks, I understand that, at least in the initial days that you were here, that you were at the--initial day or so, you were at the General Hospital site?

MR. PARKS:

A. Yes, I was.

COFFEY, Q.C.:

Q. Where the immunohistochemistry lab is.

MR. PARKS:

A. Yes.

COFFEY, Q.C.:

Q. If we could, please, Exhibit P-3119, 31-19? Gentlemen, this is entitled--a document entitled "Process Review of Eastern Health St. John's Health Sciences Centre and St. Clare's Mercy site, pathology laboratories. September 28th, 2008." Prepared by Bryan Hewlett and William Parks. Gentlemen, I just going to take you to the--review this in some detail, but there on the last page, it's written, "we believe our observations and the information presented in this report to be accurate and unbiased," and you both signed this report?

MR. HEWLETT:

A. Correct.

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MR. PARKS:

A. That's correct.

COFFEY, Q.C.:

Q. And provided it to the Commission. If I could, please, the second page of the report indicates the following, and I'm going to point you to various parts of it and then ask, depending upon what the subject matter at that particular point is, both of you to comment, one or other of you, or both, to comment upon it. Page two indicates "a review of Eastern Health St. John's, Health Sciences Centre and St. Clare's Mercy site, pathology laboratories, was conducted over four days between September 26th, 2008 and September 30th, 2008. The review was a process of observation, questioning of staff and examination of the resulting product of each of the different work areas in the histology laboratory. Particular attention was directed to the pre-analytic processes used to prepare a tissue specimen for sectioning prior to staining and examination. The new laboratory policy and procedure manual was reviewed by both Bryan Hewlett and Williams Parks prior to

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the visit. Based on the contents of this manual, a significant number of questions were developed to ask staff. Observations of the first day of the visit were confirmed, when necessary, through the development of additional deeper probing questions that were asked on subsequent visits to each site. We found the staff to be very forthcoming and honest in their answers and dedicated to the jobs and tasks they were performing." And that, I take it, in a broad strokes way, summarizes your approach and the attitude of people that you dealt with here?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. The next page deals with fixation and then we go on to the following page, on page four, processing. Mr. Parks, I'm going to ask you, in terms of kind of your general recollection of what happened in your first day, your approach. Perhaps you could tell the Commissioner your approach at the General?

MR. PARKS:

A. When I get to an institution, I like to follow

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the work as it comes through.

COFFEY, Q.C.:

Q. And if I could, before I--because I haven't done this. You've done this before, haven't you?

MR. PARKS:

A. Yes, I have. I quite often have been hired by laboratory management and stuff to go in and review an entire lab and make recommendations, and I usually do it in a two to three day flow and then make a recommended report and they will make changes to their laboratories based on that.

COFFEY, Q.C.:

Q. How often have you done this before?

MR. PARKS:

A. I've done it on three very large occasions, and I do a lot of sort of ad hoc where people will call me to ask very specific, like this section of our lab isn't working, and the staff then gets in touch with me on an ongoing basis to continue the improvement that I've recommended.

COFFEY, Q.C.:

Q. And Mr. Parks, in terms of then an approach to

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this, you have, I take it, an approach that you have mapped out in terms of -

MR. PARKS:

A. Yes, I do. I have a very -

COFFEY, Q.C.:

Q. Systematic.

MR. PARKS:

A. - systematic, exactly. I go in and I follow the work through. I study each thing and I also have learned, over time, how to reword questions to ask different people the same question, to find out if we're getting the same answers, because not everybody will always give you the same answer to the same question. So I have quite a different approach, and that's one of the reasons I do it on a two and three day thing, because you can readjust your questions the night after the first review and go back in and concentrate on things where you think there may be a problem, but you're not absolutely sure.

COFFEY, Q.C.:

Q. So if you could then, what happened then? I take it on Friday, September 26th -

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MR. PARKS:

A. Yes, Friday, we went in and I followed how the specimens flow through the lab, and I went to the different areas and was looking for all of the--every aspect of documentation and recording and what was being recorded and then I also watched the technique in use, and I followed specimens through the lab, and observed them, and then I also asked questions at each spot, how they were doing it, where they got their information, and you know, tried to figure out exactly where the information that they were using, how they were performing the work with regards to, you know, the standards of practice, and I followed it all the way through the lab.

COFFEY, Q.C.:

Q. And I'll be taking you to the various particular parts of the report that was subsequently prepared, but what do you recall about the first day generally?

MR. PARKS:

A. Well, I recall that there was--the first thing, I was actually impressed was that there was a significant amount of documentation

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going on. People recording stuff. There was stuff being signed in, and although somewhat chaotic because of the lay out of the lab, because the flow wasn't natural, it's coming in one room and crossing halls and stuff, but overall, I saw that they were--there was a very systematic approach to it, and there was the documentation and recording going on as they were doing it, and when I followed it through to the dissecting area, I was--I think the thing I was most impressed with right away was there was a pathologist interacting with a PA in the dissecting of a large specimen, and there was good interaction and then good advice on how to proceed.

So I was seeing a lot of things that you like to see, and again, I observed the dissecting of the specimens, both large and small, and was seeing that they were cutting the specimens to the right size. There was, again, standards of practice have obviously been--they're following what is recommended. They're cutting stuff thin enough for proper fixation and again, I also noticed that the recording on requisitions of time of receipt,

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time in fixation, time of processing. So there is definitely a chain of information that could be used to detect exactly how long the tissue had been in fixative, and it was 24 hours for almost everything, it not more, which I was glad to see. That's a very important point in the overall process of histology.

COFFEY, Q.C.:

Q. And then? In the PAs section, the -

MR. PARKS:

A. The PAs, it was good. I went into the--they then have--they process, the processors, I observed the processors. They were already emptied at that time, and I do my usual little checks that I do on equipment. Like I said, I work on a bench, so I do this at my own place all the time, and I had noticed that the smell when I opened the chamber of the processor was a little high for timing, and so I took note of that, but wanted to confirm it the next day. That's why we went in at 5:30 in the morning on Saturday, to be there when the machine was unloaded. I followed the specimens to the embedding area and I watched

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the process. Again, a very good flow of information. There was a document that came with the specimens that had pictures for the technologist embedding to be able to refer to, so that if there's a question, if there wasn't enough pieces there, they could go and talk to the PA or whoever had dictated it. These papers followed the specimen along with the information and little notes made by the PA if there needed to be some kind of orientation or something, which is extremely good pattern of practice, in my opinion. Having the information flow along with the specimen is vital to a good product.

I did notice at that time that the cassettes were being put into a warm well that did not contain molten wax, which to me was--I wonder if it was a one-time thing. Again, I took a note, so we could see the next morning. This is one of the ways I process. We always go back to check in case there was a one-time event. There should be - the tissue when it comes off the processor is in a - the tissue is full of molten wax, which needs to stay in the tissue for it to be properly cut and

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processed from that point forward, and by putting it into a warm well, the wax actually drains out and it leaves spaces in the tissue. So I took note of that. I noticed that the well was empty. I watched the technique, and again with the information available, they're able to do a very good job in their embedding process. I followed it from there to the matching with the slides and I then followed through into the cutting area, and was watching the people cut and taking notes on the quality of their sections, and noticed again that they were making documentation not on the same sheet of paper that came through the - at this point, the information that was used at embedding and then went through to make the slides and stuff got separated from the blocks and went over to the staining area. So the information they were recording at the microtomes, at the cutting area, was being recorded in another binder, but again there was good documentation. They had the exact cases, they had notes when they had trouble cutting the blocks. So there was information available. They were making observations and

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basically QC observations, "this is cutting difficult" and "sections weren't cutting well" and stuff, but that information was not put onto the sheets that went further on with the slides. I then watched the staining area where again they QC with proper QC slide after each change of solution on the stainers, and the slides were reviewed by a senior technologist in the next aisle, who then told them to continue on if the stain was adequate. The slides came off the machine were visually checked to see that the stain looked good, they weren't checked under the microscope, but they were visually checked, and were matched up and shipped off to the pathologist at that point. At this point, the sheets that had followed along had comments written on them and I noticed by reviewing these sheets that you could tell from that sheet which PA had cut it, you knew which processor had been on, which I thought was a good piece of information, you know the staining run it was on and that the QC had been checked. So there's good documentation and a good start of a QC program. That's - after the slides left

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the lab, I didn't follow them to the pathologist at that point.

COFFEY, Q.C.:

Q. Now that would be - this cutting and staining was in the General histology lab?

MR. PARKS:

A. General histology, yeah.

COFFEY, Q.C.:

Q. Did you - I understand that the cutting of slides and the staining for IHC is in a -

MR. PARKS:

A. It's in a separate area, yes.

COFFEY, Q.C.:

Q. Did you go there?

MR. PARKS:

A. Yes, I did. I was asked to go in. They wanted me to see what they were doing, and they have their own microtome in there, and they do their own cutting which I think is good because there's a certain QC happening - one thing I like in histology is when you can follow your work along, which is not always possible in a large institution, and that - but when you can follow your work along, you're QC'ing quite often along the way. So

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they were cutting their own slides, they were staining, and when I got there, I observed the pathologist reviewing all of the slides with the technologist on a multiheaded scope, reviewing the controls and that of the day. They walked me through - the process had finished for the day, but they walked me through their machines and asked me to look at some of their control slides and see if they had good tissue on the slides.

COFFEY, Q.C.:

Q. And did you do so?

MR. PARKS:

A. It is not as extensive as I use myself, but it is definitely - it is a QC program that is - it's growing at this point. They do have each slide is being controlled and there is a positive piece of tissue on the slide that runs along with it, and that to me is step one in QC'ing of immuno.

COFFEY, Q.C.:

Q. Now the - does that then take you through your first day?

MR. PARKS:

A. That was my first day, yes.

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COFFEY, Q.C.:

Q. Perhaps I could ask you, Mr. Hewlett, to recount your first day. I take it you were at St. Clare's?

MR. HEWLETT:

A. I was at St. Clare's, yes. I looked at the physical plant which, of course, is more restricted at St. Clare's because they basically only have grossing and specimen entry, although they do some quick sections and very fortunately a quick section was called while I was talking to one of the pathologists, and I asked if I could go to the operating theatre and observe the quick section. It was already in progress when I got there. Another pathologist had prepared the tissue in a most appropriate manner. It was a fairly large piece of tissue. It was sectioned. It had been marked for locations and margins and was very nicely sectioned out, the appropriate thickness, and it didn't end up actually having a section because there was no obvious area to section, but impression smears were made which is an excellent technique and it was really quite impressive,

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very smooth. There was a technologist up there who had the excision numbers ready for this specimen and the cassettes for the pieces to be sent for fixation, and I watched that happening. Back down in the laboratory, I tracked the PA and again observed what they were doing in the grossing area. They were following the procedures in the procedure manual, which is always good. Again another very lucky circumstance, a breast localization specimen was sent and I got to observe most of that process, not all of it, because some of it occurs in mammography. They take images, location of the wire that the surgeon has placed in, but I observed that entire process and again it was exactly as the manual suggests it should be, without reference to the manual, I might add, but I questioned the PA and they could quote the procedure basically step by step.

COFFEY, Q.C.:

Q. From the manual?

MR. HEWLETT:

A. From the manual. They obviously were very familiar with this, and unannounced, one of

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the pathologists arrived to see if they could be - if he could help in any way in terms of the localization. So again I observed, as Bill did, a really good interaction between the PA and the pathologist in the handling of this sample. I watched some more grossing for the rest of the day and then followed those specimens back over to the Health Sciences to be processed.

COFFEY, Q.C.:

Q. How did that work?

MR. HEWLETT:

A. I have a little bit of concern in terms of the safety. The cassettes are loaded in a tray, a small volume of fixative is added to keep them moist and they're double wrapped in a plastic bag and delivered by cab. There's always a danger that the cab is involved in some kind of an accident, there could be spillage, and the tissues could be compromised. So I think I would have liked to have seen a better shipping container and a double wrap, but things went without incident, and it's not uncommon for people to do it this way. I did observe that the cassettes when they arrived

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at the Health Sciences were then reassigned to processing tray. They have a really interesting system of organization for processing tissues, prioritization, and everything is very highly organized and diagrammed. It's a great QC practice. I was quite impressed by that, but was concerned at the number of cassettes being placed in each compartment of the processing tray. There is space for approximately ten and they were - all the spaces were full. That is of concern because these cassettes have holes in them so that the reagents can flow through and contact the specimens. There is a danger if you squeeze too many cassettes together in a stack that the holes won't line up.

COFFEY, Q.C.:

Q. And you won't get the proper flow?

MR. HEWLETT:

A. You won't get the correct flow processing reagent, so we suggested to them that perhaps they could just remove two cassettes from each compartment and now the cassettes can rattle around. There is a turbulent flow in the processing machine which will allow the

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cassettes to rattle around in the compartment without losing their order and position, and that is preferable.

COFFEY, Q.C.:

Q. Go ahead.

MR. HEWLETT:

A. And that was - I had a look around the Health Sciences just briefly to determine what I was going to concentrate on the following day. It was very apparent to me when I walked into the tissue processor room that there was an odour of xylene and one wonders of that. So without having not talked to Bill at this point, I pulled out the processor drawer and the odour of xylene was just huge, so I did a combination of finger test and nose test, which one is not supposed to do, you're not supposed to inhale toxic fumes, but it really is a quick way of finding out. At my age, I've probably inhaled all the toxic fumes I'm going to, so I had a quick sniff on the fourth wax container, which is the cleanest, and it had a level of xylene in it which was way in excess of what I would expect in the first wax, which is the most heavily contaminated

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and then I dipped my finger in and checked the consistency of the wax. It was greasy.

COFFEY, Q.C.:

Q. I take it, it shouldn't be?

MR. HEWLETT:

A. No.

COFFEY, Q.C.:

Q. Okay, and how should it feel? You say it was greasy.

MR. HEWLETT:

Q. Well, one lets it solidify on the fingers and then just rub them together and it feels like candle wax, not sort of a liquid oily component to it.

COFFEY, Q.C.:

Q. Which is what you -

MR. HEWLETT:

A. Which is what I could feel. One expects that in perhaps the first wax.

COFFEY, Q.C.:

Q. Mr. Hewlett, then what happened? I take it that concluded your first day.

MR. HEWLETT:

A. Yeah, pretty well at that point. Bill and I had some discussion as to what we had observed

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because we were trading places the following day.

COFFEY, Q.C.:

Q. And if I could then, Mr. Parks, could you take up the account then, what happened the next morning?

MR. PARKS:

A. The next morning.

COFFEY, Q.C.:

Q. This would be Saturday morning.

MR. PARKS:

A. Saturday morning at 5:30 we were there when they downloaded the processor.

COFFEY, Q.C.:

Q. That was "we", the -

MR. PARKS:

A. Both of us. We went together because St. Clare's is not open on Saturday, so we went together and because we compared notes, we kind of did a different approach. We observed them unload the processor and again the baskets of cassettes were put into empty wells, heated wells on the embedding centre.

COFFEY, Q.C.:

Q. And how should the wells -

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MR. PARKS:
A. They should be full of liquid paraffin. The tissue should be sitting in paraffin for the time that they're being embedded because the embedding process is slow and these cassettes could be sitting in that well for up to two hours. Two hours in a heated environment with the molten wax in the tissue, it's running out of the tissue, and they should be suspended in molten paraffin.
COFFEY, Q.C.:
Q. In a bath - effectively in a bath?
MR. PARKS:
A. In a bath, exactly, and these chambers are heated to the temperature that will maintain paraffin in the liquid state as it should.
COFFEY, Q.C.:
Q. So, therefore, if it's there in a chamber heated to that extent, but no molten paraffin, no bath -
MR. PARKS:
A. Yes, its draining out.
COFFEY, Q.C.:
Q. The paraffin that's already in the tissue is hot enough literally just to drain away?

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MR. PARKS:
A. Yes, it does, and you can see afterwards -
COFFEY, Q.C.:
Q. We'll talk about that.
MR. PARKS:
A. We were watching after they finished and we noticed quite a bit of paraffin because they wipe the chambers out quite cleanly, but after they finished embedding, there was a good layer of wax on the bottom of the hot chamber. So that wax came from - obviously from the cassettes that were sitting above it for that period of time. At that point, we also reexamined the processor.
COFFEY, Q.C.:
Q. And if I could, just on the point talking about the wax, and I will be returning to this, the processor - tissue processor, itself, when the tissue comes out in these cassettes, is already impregnated with the wax at that point, I take it?
MR. PARKS:
A. Correct.
COFFEY, Q.C.:
Q. A sufficient amount of wax.

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MR. PARKS:
A. Yes.
COFFEY, Q.C.:
Q. If the processor is working properly -
MR. PARKS:
A. Yeah.
COFFEY, Q.C.:
Q. In the tissue with that.
MR. PARKS:
A. Yeah.
COFFEY, Q.C.:
Q. And, in effect, by laying it out in a heated but clean chamber -
MR. PARKS:
A. The wax is leaving the tissue. So you're leaving spaces in the tissue that will not be supported correctly during the cutting process. So the wax is coming out and the wax is actually what supports and protects the tissue after the whole process.
COFFEY, Q.C.:
Q. Go ahead, Mr. Parks.
MR. PARKS:
A. So when we reexamined the processor, we opened the chamber and the fumes were extremely high.

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We checked all the waxes and they were at the point that I was quite concerned. I was. We discussed it. Again Bryan checked it independently, did the same check, and I always do the same sort of check. I always check the quickness that the wax will solidify on your finger indicates the amount of toluene that is in the wax, plus the - I did not put my nose near it because I didn't need to. As soon as you open the oven, the fumes of toluene is extremely high. So we took note of this and we were glad that there was not another run being set up on the Saturday because they do not run their processor over the weekend. They run it Friday to Saturday morning. They come in and embed, and that's all the work that's done there that day. So the processors were not going to be used that night. We stayed with them during the embedding process and watched again the use of all the documentation and proper orientation and stuff, and at the end of that, it was around noon that we were finished there for the day, and that was the end of the day. That's when we had a long discussion. Knowing

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our mandate was to observe, we had a discussion to decide how should we proceed because we were not there in - in my usual capacity, I intervene in a hospital. This was not my capacity here, so we were - it was a ethical dilemma which went on for a while and we finally decided that we could not let the processor run again that day.

COFFEY, Q.C.:

Q. So what then happened?

MR. PARKS:

A. I contacted you to ask if we could step outside the - our mandate, and actually make an immediate recommendation to the hospital on Monday morning so that, you know, the processor could be run properly.

COFFEY, Q.C.:

Q. And what did you do, what were you told, and what did you do?

MR. PARKS:

A. We went back on Monday morning and Bryan went and spoke with the manager and told him what we had determined and made the recommendation that everything on the machine be dumped and changed so the processor would be fresh and

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clean for that night's processing room.

MR. HEWLETT:

A. If I may, Commissioner, we had also checked the schedule reagent change documents and one machine had had two runs and the other one had had one, and that raised more concern.

COFFEY, Q.C.:

Q. Why is that?

MR. HEWLETT:

A. Well, the machine with only one run had actually had less tissue through it, so normal carry over should be less, and the smell from that machine was just as strong as the first one. So then one wonders, well, did the changes occur. Although they're signed off on a sheet, and I tend to be a little suspicious sometimes, or is there a real problem with the equipment, and we spent some time actually calculating carry overs and trying to figure things out. There was obviously a problem.

COFFEY, Q.C.:

Q. So you did intervene on Monday morning before there was --

MR. HEWLETT:

A. Absolutely.

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COFFEY, Q.C.:

Q. Before there was any further processing on those machines?

MR. HEWLETT:

A. I spoke both to the histology manager and to Mr. Gulliver, who's the director of laboratories, to tell him that we felt this was serious enough that something should be done urgently before the machine is used. Fortunately, at this point we were pretty well aware that the tissue to this point was now well fixed.

COFFEY, Q.C.:

Q. Well fixed before it ever came into the -

MR. HEWLETT:

A. Before it even comes into contact with the processor and that is key because the reagents that the tissue goes through following fixation produce a large amount of damage if fixation is not adequate, but we knew that certainly the material we had observed going onto that process was appropriately fixed. SO that mitigates any - but still it's a concern.

COFFEY, Q.C.:

Q. And why is that? Why is the effect or

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potential negative effect or effects of what you observed this - well, the deficiencies in the processor, what's the effect potentially on the tissue?

MR. HEWLETT:

A. The most obvious effect of a solvent in the wax occurs during cutting. Let me back up a moment. After embedding, the wax is solidified. With a percentage of solvent in it, it will be softer, of less support to the tissues and if there's enough of it, the technologist will be hard pressed to even obtain a section. You need the rigidity of that wax to support the tissue during the cutting process. The cutting process generates a couple of thousand pounds per square inch, the knife edge, and the wax with a little solvent in it will simply collapse on the knife edge, compress, so you can't obtain a section. If there's a little less solvent, you can obtain the section and then the next step in the process is to place that section, float it onto the surface of warm water to remove any wrinkles and creases and to flatten the section out ready to pick it up on a glass

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slide. The moment you put such a section on the warm water, it will literally explode. It just disintegrates.

COFFEY, Q.C.:

Q. If it has too much of this chemical?

MR. HEWLETT:

A. Absolutely. The wax which is holding it together will suddenly disintegrate, and the actual tissue may still be intact, but probably damaged. So this is of some concern.

COFFEY, Q.C.:

Q. And if I could then - and I'll take up that narrative again, okay. You on Monday, the following Monday, which would be the 29th, I believe, of September, if I could ask yourself and Mr. Parks then - you have already indicated you had gone to the General Hospital lab that day to speak about the tissue processors. I take it there were two of these?

MR. PARKS:

A. Pardon me?

COFFEY, Q.C.:

Q. There are two of these tissue processors?

MR. PARKS:

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A. Yes, two tissue processors side by side, yes.

COFFEY, Q.C.:

Q. And you addressed the issue of the tissue processors with the individuals you've identified. What then happened throughout the day in terms of yourself?

MR. PARKS:

A. Well I went over to St. Clare's at that point to observe the process at St. Clare's.

COFFEY, Q.C.:

Q. And what did you find there?

MR. PARKS:

A. Again, it was a very interesting thing--a technologist who had not been to St. Clare's before was asked to go over and cover quick sections. And when she got there, there's a quick section right away, but the documentation and everything was so well laid out, she was able to walk into a lab that she had never been in before and perform a quick section immediately. Because of the way the procedure was laid out on the bench, she was able to do all of the entry into the computer and stuff that she had never done before, but the manual or the section of the manual for

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that was so well written, she just went right through it and was able to do the quick section quickly and efficiently and I was quite impressed because someone who is put into a laboratory that they had never been in before was able to do it so efficiently was a good sign to me that she knew what was she doing, but also the documentation and the manual was present to assist her.

COFFEY, Q.C.:

Q. And then as the day went on in St. Clare's?

MR. PARKS:

A. I went and spoke to Dr. Denic and told him about what we had discovered over at the Health Science Centre and told him that we had intervened and I had told him that I had contacted you to ask if we could, and he thanked me very much for having actually done that. He said, you know, we realize why you're here, but first and foremost is patient care and he really appreciated our effort to get the situation corrected.

COFFEY, Q.C.:

Q. And anything else? You spoke to Dr. Denic and -

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MR. PARKS:

A. I was there, again I went to the grossing area and I observed there at the grossing area, again a PA who was just starting there from the other site. They have a switch around which I think is a very good idea, that they all get different experience and she had the manual present and she was dissecting specimens and again, I got out my little eyes and looked at the thickness of tissue and stuff and she was really in the limits, nice size tissue. Again, the thickness of tissue and size of tissue is critical in the overall processing of it. Larger pieces of tissue that are crammed into cassettes, again affect fluid flow around them and it does inhibit the proper processing. So having specimens of proper thickness for fixation and processing is critical and they are really doing an excellent job at that in the PAs' area.

COFFEY, Q.C.:

Q. And did you observe anything else at St. Clare's that day?

MR. PARKS:

A. No, I came back over to the site, to the

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Health Science around 1:00 and started to observe some things in there?

COFFEY, Q.C.:

Q. And what did you see there?

MR. PARKS:

A. I went into the lab because they were training some new technologists and again, what I was seeing was a lot of technologists in flux, you know, being training on one specific bench and put on a bench for a period of time and I wanted to confirm this because I had seen it on Friday and I got this information from people, "I'm only here for a certain period of time. I'm only there for a certain period of time." And I wasn't seeing a stable staff and I wanted to investigate this further because we knew there was a new technologist who just graduated who was really eager to be in histology and I wanted to see how she was being trained and I wanted to see and talk to other technologists and get a feel for their length of time and experience in the lab. And I was finding a lot of people that had been there for a period of time and left for a period of time and come back, there was--I

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couldn't find a solid core of staff that wasn't in flux and that one of the things with histology is the training process really should be one of the same way the tissue flows through, the understanding of the process and what's going on in the whole lab, you need to follow it through to see why you're embedding a certain way, why you're cutting a certain way. And I was finding technologists that had been just put on the bench because they knew they were going to be there for five months, so they were trained in an area where they could get maximum utility out of the staff without having to train in a lot of different areas. And I came across one girl who had been there for a pregnancy leave and had basically only been doing cutting and quick sections and no other involvement into the lab. So that's what I--I spent a lot of time just walking around and looking at the training that was going on and there was two people--this was, I found very--this was the bright spot for me, was there was two new techs who knew they were going to be permanent and they were being trained from the gross

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room all the way through the whole process and we were witnessing that and I thought that was a good start. But then I came across many other people who were not, who were just--who knew they were on their way out and they said, well I'll be back over in another area soon and so that was what I really wanted to investigate that, just to get a feel for why there wasn't sort of continuity. And that's why I spent a lot of time just talking and not even asking specific questions about that, but asking other questions to get a feel of their knowledge of what they were doing.

COFFEY, Q.C.:

Q. And what did you find?

MR. PARKS:

A. I found that on the benches they were on, they had knowledge of what they were doing, but there was a disconnect between the rest of the work coming down. So along with the disconnect of, your sort of knowledge goes the disconnect of quality control. Quality control is a total process is histology and in any lab where you need to have the quality checked along the way and you have to

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understand what's happened before you to be able to do a really good QC at the point you're at. And that was the thing I was finding, they were being given quality control jobs, but they weren't all put together, so there was a lot of QC going on at each individual spot, but it wasn't being tied together and the information that was being generated was not being used to modify a previous process. And one of the interesting points and it goes back to what Bryan had said about the tissue exploded on the waterbath. Most hospitals, most places I've ever been to, we all do our tissue floatation at about 45 to 46 degrees, the water temperature is 45 to 46 and you get, if your wax is clean and it is properly processed, it floats out very nicely at that temperature. We found that all the waterbaths had been set to 42 degrees and this would compensate, by lowering the temperature, your tissue would not explode so quickly, and that was a sure sign that they knew how to make a correction, but they were making the correction at the wrong spot--they were getting better sections because they had

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cooled their tissue--cooled their waterbath. Had they, you know, walked back through the process and this is one of -

COFFEY, Q.C.:

Q. Had they walked back through, I take it, they would have figured out, well there's something about this tissue that requires us to lower the temperature -

MR. PARKS:

A. Exactly, yes.

COFFEY, Q.C.:

Q. That shouldn't be happening, therefore there's something up -

MR. PARKS:

A. Up stream.

COFFEY, Q.C.:

Q. Up stream.

MR. PARKS:

A. And that is exactly what pathology is all about and we're finding that the people are knowing that there's something, but it's the connection of everything back together in a total QC, QA, quality assurance, and what we've referred to as total quality management. It's a continuous flow of information between

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every area and if that isn't happening, you're not making adjustments at the right spot. You're treating a symptom as opposed to treating the cause, and that's what we're seeing with the disconnect of information and again, it comes down to if you haven't been trained through everything, you know, you act at where you are. With your knowledge as a technologist, I've got to do something to make this good, it's not always--it does the best for the patient at that spot, but it's the total QC program that has to come together and bring all information together and that's the disconnect I was finding and I think it's because the staff, as dedicated they are, don't--but because you're moving in and out of the place, you don't acquire the knowledge that you need and histology, as we're finding, more and more is being asked of histology by our clinicians and our surgeons and stuff. And you have to stay, it takes a long time to develop all the knowledge and stuff in histology. It's not a push button type of science, it's a real hands-on and it's a skill, it's a dexterity skill and there's a

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lot of skills involved that take time to develop. And, you know, in my lab I don't let people who are more than, they have to have five years of experience before you want to have them even teaching other people. There's a long learning curve in histology and you can't do it if you come in for three months and then disappear sort of thing. So that was what I spent a good part of my Monday afternoon, just talking to people and finding out where they had been and where they were going and a lot of them knew they were leaving within a certain period of time, which was unfortunate because you could see there was some eagerness but they knew they were leaving, so that was -

COFFEY, Q.C.:

Q. Mr. Parks, on Monday--you've referred to the fact that when you went to St. Clare's earlier that day, you had noticed the procedures for this quick section that this person coming into the lab had it all laid out in front of-- I think it was a her -

MR. PARKS:

A. Yes, it was.

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COFFEY, Q.C.:

Q. How did what you saw at St. Clare's in relation to the documentation, the policy and procedures manuals and having it all kind of readily available and spelled out and at hand, compare with what you saw at the General Hospital in relation to that and perhaps you can tell us about that?

MR. PARKS:

A. It was interesting because the information I got on Friday and the information I got on Monday conflicted with regards to the documentation at the Health Science Centre. There is--they are working on this new manual and it is a very well written manual, I think it's excellent, but the people over at St. Clare's are reading it and signing off on it and the technologists that I went over to St. Clare's with, even went to the manual to check what she had read and I said to her because she was at the other site, I said, you knew about this manual? She goes, "Yeah, there's one in the lab." But on Friday I had asked and most people were not aware of this new manual -

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COFFEY, Q.C.:
Q. At the General Hospital site.
MR. PARKS:
A. At the General Hospital they weren't aware of it. And I said, well where is it located because I had been shown the master copy in one room and she said, it's out in the lab. So when I got back, sure enough I went straight away to where she had said it was and it was there.
COFFEY, Q.C.:
Q. This is in the General Hospital.
MR. PARKS:
A. At the General Hospital there is a manual out in the laboratory and it is the--it's broken down into sections and I had asked and a lot of them weren't aware that it was there.
COFFEY, Q.C.:
Q. You had asked on Friday, a lot of the technologists -
MR. PARKS:
A. A lot of the technologists did not know about this new procedure manual. But obviously a few did because this girl that--the technologist that took me to St. Clare's, she

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knew about it.
COFFEY, Q.C.:
Q. She knew that it was at the General too.
MR. PARKS:
A. She was at the General, she had been located at the General for the last little while and she knew it was there. She said, "Oh yeah, it is present." And sure enough it was there and it's well--it's divided up and it's there, but it has not, I don't believe, been rolled out to the staff in a way that they've been told that this is our new Bible of Procedures, which is basically what a procedure manual is in a hospital. It's how you operate and it's there, it's well written and it just needs, the staff needs to be brought on line with it at that campus.
COFFEY, Q.C.:
Q. Now the General Hospital in relation to the immunohistochemistry service which is, as I understand, in the main three technologists, in IHC there are three techs.
MR. PARKS:
A. I believe there's a fourth one trained now.
COFFEY, Q.C.:

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Q. A fourth now perhaps being trained and they're off to themselves, as it were.
MR. PARKS:
A. Yes, they are.
COFFEY, Q.C.:
Q. Compared to the rest of the histology laboratory.
MR. PARKS:
A. Yes.
COFFEY, Q.C.:
Q. What did you find our observe about the IHC part of the lab in terms of their usage of these new policies and procedures written? Were they aware of -
MR. PARKS:
A. Oh they were very much aware of it. There's almost a different culture between -
COFFEY, Q.C.:
Q. Yes.
MR. PARKS:
A. There's a different culture between the IHC lab and the main lab. IHC, I guess they're all there, they know they're there, they're staining there. There's this eagerness to learn. They know their manuals, they can

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quote big chunks of the manuals, they follow them explicitly. They're aware of everything in there, but it's a core group and they are dedicated and I think that's the thing is that they knew they're going to be there, so they are very different in their attitude towards stuff, they are very clued in and learning. And that's the other thing is is there was good interaction with the pathologist. The pathologist was there both days I was there or actually all three times we were there, he was there, except on the Saturday. He was there with them, he's reviewing slides with them, so there is good interaction. There's a good cohesive group and I think that's the key. They know they're there and they're staying and they're very different than the main lab in the connection of information and stuff.
COFFEY, Q.C.:
Q. Now in relation to IHC verses histology generally, I take it that the IHC technologist in doing their work, of course, utilized blocks -
MR. PARKS:
A. Yes, they do.

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COFFEY, Q.C.:
Q. Paraffin embedded--paraffin wax blocks of tissue to perform their procedures.
MR. PARKS:
A. Yes, they do, they cut their sections off those blocks.
COFFEY, Q.C.:
Q. So all the IHC's and that would include ER and PR?
MR. PARKS:
A. Yes, it would.
COFFEY, Q.C.:
Q. And any other IHC staining.
MR. PARKS:
A. Exactly.
COFFEY, Q.C.:
Q. The blocks, who produces the blocks that they rely upon?
MR. PARKS:
A. The histology lab produces the blocks. When the pathologist sees the H&E produced in histology the request for the immuno goes to--and they go and get the blocks and bring them into their area to work with.
COFFEY, Q.C.:

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Q. So the immunohistochemistry of a laboratory, whether in the General Hospital or anywhere else for that matter, the IHC part of the lab does not produce its own blocks, they reply upon the skill and attention to detail of the other histotechnologists.
MR. PARKS:
A. Histology lab, exactly, yes.
COFFEY, Q.C.:
Q. And I take it then generally if there are short comings in histology, processing of blocks, there's not really much immunohistotechnologist can do about that to correct that?
MR. PARKS:
A. They have to work with the block that is provided. One thing is I do know that there is when they have, at the cutting, if they have some--there was procedure in place for reprocessing, so that if they detected the block was not good at cutting, it could be reprocessed and be made better. I did not witness that being used, but I do know that there is in the manual a section on that. So if at cutting you detected a bad, a block that

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was not good, you could send it for reprocessing and then it would be a much better block for the next steps, all of your ancillary studies.
COFFEY, Q.C.:
Q. And this reprocessing would occur in the histology section?
MR. PARKS:
A. Yes, it would.
COFFEY, Q.C.:
Q. And although if it was being reprocessed on a processor that wasn't working properly, you'd have, in effect, get the same thing again.
MR. PARKS:
A. Exactly, you would.
COFFEY, Q.C.:
Q. Now did you do anything else on Monday, yourself? You were back at the General and you were questioning people?
MR. PARKS:
A. I sat down after I finished questioning that, the immunohistotechnologists and the pathologists wanted us to spend some time looking at their controls again and looking at their immuno that they had produced that day

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and so we went to the ten-headed scope with the whole immuno team and the pathologist and we reviewed slides with them and commented on quality and, you know, gave them advice on different things like quality control block, what would you want a little more of this in there, different types of tissue. So it was kind of after the thing, they asked us if we would come and look at this stuff. We were asked if we could sort of just to help them a bit and share some of our knowledge. So we spent at least an hour sitting with them. They were taking notes and very good conversations of how to proceed and how to build really good control systems and how to improve on what they're doing and stuff like that. So it was more of a sharing of knowledge session. It was a little outside of what we were there for, but we had done our assessment and we felt that if they wanted this information, it was fair to share it with them.
COFFEY, Q.C.:
Q. Mr. Hewlett, can you tell the Commissioner then what you did on Monday? You recounted

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how initially you went and spoke to the director about the processor, what then happened?

MR. HEWLETT:

A. I wanted to track the progress of the blocks we had seen embedded on Saturday. So, I went to the cutting stations and observed what was going on there. And there were definitely signs that the tissue was not fully processed.

COFFEY, Q.C.:

Q. You say not fully processed, what does that mean in this context?

MR. HEWLETT:

A. It means that there is evidence of xylene and contamination in the wax. That's not fully processed. Independently, Billy, who had already asked the question, I asked about the floating out bath water temperature, sure enough it was down and I queried the technologists if they had any problems with microtomy. Other than what was marked on their documentation sheet and they said, oh yeah, you know, very often the sections will blow when they hit the water. And I said, well, you know, you haven't got this marked

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down on the comments. Oh, but that's common.

COFFEY, Q.C.:

Q. It's a common occurrence?

MR. HEWLETT:

A. Yes, a common occurrence which is why, of course, they're turned their water baths down. But there was some comments there that said, fatty tissue difficult to cut, that sort of thing. So, I went back and looked at these blocks and one of the effects of contaminated wax, contaminated with xylene is that, of course, it will evaporate over time.

COFFEY, Q.C.:

Q. That is the xylene does.

MR. HEWLETT:

A. As the xylene and the end result is that the surface of--the cut surface of the block and the tissue will sink, it retracts, becomes saucer shaped as the solvent evaporates. And there was evidence of that starting to happen. So, I went to the block files and I knew that the processors were really new, so I went to the block flows and randomly checked blocks in storage since the new processors were in place. And on a regular basis, all large

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pieces, by the way, large pieces of tissue--I could pull a block and it was something in it. And sometimes the surface of the tissue, instead of being polished and being sunken in, it was rough and dry.

COFFEY, Q.C.:

Q. And what does that tell you?

MR. HEWLETT:

A. Well, that tells me that there may also have been a problem with the dehydration. Unless the tissue is dehydrated, they xylene can't penetrate the tissue.

COFFEY, Q.C.:

Q. The dehydration occurs in the tissue process itself.

MR. HEWLETT:

A. In the tissue processor, it's an earlier stage and some of them were dry. Some of the blocks, particularly those that really were fatty, had greasy feel to them. And that is due to the fact that the xylene has not removed the normal tissue fat appropriately. And that would sort of fit with insufficient dehydration causing insufficient clearing and hence, insufficient infiltration with wax.

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So, it sort of piles problem on problem.

COFFEY, Q.C.:

Q. What can cause insufficient dehydration to occur?

MR. HEWLETT:

A. If the tissue is too thick.

COFFEY, Q.C.:

Q. Too thick.

MR. HEWLETT:

A. Yeah. The processors are set, obviously they have a program and the program should be designed to accommodate a certain thickness of tissue. We know the penetration rate of reagents and one can calculate how long in each reagent to stay (phonetic). And it's because of the nature of the modern clinical laboratory, everyone is very focused on turnaround time. And so most modern processors are set to, in my view, short process which means that there is a responsibility to put thinner pieces in. And this is done to get the tissue ready to cut the following day.

For instance, Bill and I were in at 5:30 in the morning which is the normal embedding

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time. In our institutions, it's 6:30 or 7. So, that's an additional hour that's been cut off the process time.

COFFEY, Q.C.:

Q. Mr. Hewlett, now these blocks that you went out and, kind of, randomly examined, they went back how far? What time period -

MR. HEWLETT:

A. Oh, I just initially examined for about eight months to 2008 which is when the new process -

COFFEY, Q.C.:

Q. The new processes were in place.

MR. HEWLETT:

A. Yes. And then I thought well, maybe we'll go back a little earlier and see if this is a systemic sort of issue.

COFFEY, Q.C.:

Q. Go back before the new processors, back to the older ones.

MR. HEWLETT:

A. Yeah, and I can't remember the date at this point, but it was some years before. Periodically I went, randomly just went up to the block files, pulled the tray and flicked through until I could see there was a large

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tissue block, pull it.

COFFEY, Q.C.:

Q. What did you find in relation to those?

MR. HEWLETT:

A. It was sunken and dried.

COFFEY, Q.C.:

Q. And what would cause that? The same -

MR. HEWLETT:

A. The same issue.

COFFEY, Q.C.:

Q. Okay.

MR. HEWLETT:

A. It's not unusual to go into a laboratory and occasionally find a block so sunken. I mean, it happens to everyone. A moments inattention during grossing and the tissue is a little thicker than it should be because they've all gone the same process schedule. And so the odd one will show this, but on such a consistent basis that I was observing here. And when Bill came back over, I was to the point that (unintelligible) there and said why don't you check a couple of blocks and I believe you found the same thing.

MR. PARKS:

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A. Yes.

COFFEY, Q.C.:

Q. So, this would be Monday?

MR. HEWLETT:

A. Yes. And later in the afternoon, after I had been around and checked documentation and checked the procedure manual, I also looked at the procedure manual in place in the lab. I asked the techs, do you have a procedure for this? Some of them were aware there was a manual, but most were not--a new manual that is. And so I went to look at it and sure enough, the opening page, there's a signoff sheet and in most institutions I'm aware of, when a new procedure is put into place or even a re-written old procedure, the technologists all are expected to read the new procedure and sign off on it.

COFFEY, Q.C.:

Q. And what did you find when you looked at this -

MR. HEWLETT:

A. There were no signatures on the sign off sheet.

COFFEY, Q.C.:

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Q. And that would be September 29th of this year?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And at St. Clare's -

MR. HEWLETT:

A. In contrast, at St. Clare's, that few people, there were a number of sign off signatures on there and actually when I arrived one of the techs was reading through the manual. They had been informed and they were in the process of reading through it and signing off on it.

COFFEY, Q.C.:

Q. That takes us through Monday. I take you participated in this conversation with the immunohistochemistry technologists.

MR. HEWLETT:

A. Oh yes and if I may add, Commissioner, the thing that--when Bill and I discussed this afterwards, the entire immuno staff, as were the PAs, by the way, were totally engaged and enthusiastic and--we almost had to fight our way out there. They were so eager for input and that's always a sign of good things, it really is. So, I would comment on that

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particularly, it was noticeable in those two areas -

COFFEY, Q.C.:

Q. Amongst the PAs and IHC techs.

MR. HEWLETT:

A. The PAs and immuno people were thoroughly engaged and enthusiastic. And there was a bit of a lack of that everywhere else.

COFFEY, Q.C.:

Q. Everywhere else in histology.

MR. HEWLETT:

A. Yes. Not amongst the pathologists.

COFFEY, Q.C.:

Q. No.

MR. HEWLETT:

A. All the pathologists we talked to were highly engaged.

COFFEY, Q.C.:

Q. What then happened--I'm going to ask you, Mr. Parks--on Tuesday?

MR. PARKS:

A. Tuesday we returned before leaving to go home, back to the lab to check the processor that had run the night before. And when we got there, they had already dumped the wax because

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they had found it to be very contaminated again. It was still -

COFFEY, Q.C.:

Q. Sorry, so this had all been replaced the -

MR. PARKS:

A. On Monday everything had been replaced -

MR. HEWLETT:

A. Yes.

MR. PARKS:

A. By the time we got there on Tuesday, he had already poured it into--it was still in the molten form. So, I was able to go in and do a finger check on it and sure enough, it was significantly slimy and the fumes of toluene coming out of the garbage was quite high. I mean, I held the garbage can and it's--so, right away, I thought, we had witnessed the change and the documentation of the change. So, we, right away, recommended that they get this machine looked at because it was--I have the same machines and we do not have that volume of contamination after one run. And I run full loads, like they do 300 blocks. So, it's very unusual for it to be that high an amount after one run. So, and I did check the

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garbage and we did the test. So, we recommended that they get the company to come in service the machine and check out. In the manual, there is a mention that there is a fume xylene system that takes the fumes out.

COFFEY, Q.C.:

Q. This is the manual for that tissue processor.

MR. PARKS:

A. Yes. I went and opened it up and we looked at it with the manager of the lab and with the technician who was working that machine. And we did follow down and found the section on the fume removal or, it's called degassing, the exact words. It's a degassing system that takes the xylene off. So, I figure if after just one run, if it was that high, that there must be something wrong with the degassing, but I'm not a service person and I don't know the mechanics of the machine, but we recommended that they have it looked at.

COFFEY, Q.C.:

Q. Okay. Anything else you were involved in on Tuesday?

MR. PARKS:

A. Tuesday, we just took a quick walk around the

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lab and again, the immuno people asked us if--they said, when is your flight? Would you like to come and talk some more and discuss some stuff? But we had to leave, so it was just a quick good-bye and that was it.

COFFEY, Q.C.:

Q. And -

MR. HEWLETT:

A. If I could add something, on the Monday when we asked them to change the machine, I also asked the technician to pour some molds labelled from each wax container on each machine and we let them solidify and I sealed them in a plastic bag and gave them to Barry, the manager, and said "you need these as evidence when your service people arrive" and later that day, he took one of them--and remember, this should have the consistency of a candle. And he gently pressed his thumb on the surface of the block and it crumbled and that's an idea of the degree of contamination. So the next day with one run through the machine, both Bill and I could detect xylene again and certainly in the first two waxes on each machine there, I asked them--or actually

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they done it, they poured molds of those two and kept those for evidence.

COFFEY, Q.C.:

Q. And then on Tuesday, there was nothing else that, other than what Mr. Parks has described, you were involved in, that you can recall?

MR. HEWLETT:

A. I couldn't tell you.

COFFEY, Q.C.:

Q. If we could, please, Exhibit P-3038? And I appreciate Mr. Parks has already indicated that, of course, he's not a technician who would service a VIP5 tissue processor and I take it you're not either, Mr. Hewlett?

MR. HEWLETT:

A. No, but I think we're both sufficiently experienced with these particular machines, actually, that you know, we were aware something was definitely wrong.

COFFEY, Q.C.:

Q. And here, this is a document, it's entitled "The St. John's Health Sciences Centre, VIP5 Tissue Process "Excessive xylene fumes". It reads, "The following is a detailed description of the troubleshooting events

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between Somagen Diagnostics and the St. John's Health Sciences Centre for the investigation of a possible cross contamination of reagents, as all paraffin reservoirs had an excessive xylene fumes. Somagen Diagnostics was notified of this issue on the morning of Monday, September 29th, 2008. The assessment was completed by Jamie Simpson, field service engineer for Somagen Diagnostics and he then goes on to describe the assessment and possible issues. The assessment indicates "On October 1st, 2008, Jamie Simpson was dispatched to do a thorough investigation of two VIP5 tissue processors"--and the serial numbers are given--"because of excessive xylene fumes from paraffin stations 13 and 14. The main contact of this site was Barry Dyer, divisional manager. The following is a summary of the information that was provided by Barry Dyer. As part of an ongoing inquiry, an inspection team was present at St. John's Health Sciences Centre cytology lab and inquired about xylene odours in the paraffin reservoirs, reporting that the smell was stronger than it should have been in stations

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13 and 14. No measurements in parts per million were taken. Possible issues, first of all a use of over a hundred sponges per day, leading to xylene carry over into the paraffin stations." The second bullet, "Charcoal filter had not been replaced since March 2008." Sub bullet, "Charcoal filters are recommended to be replaced every 20 processing runs as they become saturated with xylene molecules." And the third bullet, "Fume control water not being replaced daily." Sub bullet, "Fume control water is part of a fume removal system and is recommended to be changed every processing run." And then it goes on to speak about instrument verification performed by Mr. Simpson in terms of what he did then to check the machinery itself. And he, under the heading "Evaluation of Instrument Verification", he notes, he concludes by saying "All program times were correct and conformed to laboratory SOP." And then he notes in paragraph (e), "The laboratory had two new charcoal filters on hand which were replaced during the warranty inspection." And when we look up in his

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report, he had done the warrant inspection himself, this day. "The laboratory was found not following the recommended maintenance for charcoal exchange every 20 runs and replacement of fume control water every run." He says then finally, "A full end of warranty inspection was carried out on both instruments"--and he goes on to talk about that at some length and then he summarizes as follows, well actually he says (g) "The instruments ran with a routine program overnight with a new charcoal filter in place, along with new paraffin baths and no xylene fumes were detected the next morning. Summary: based on the inspection performed and information gathered by Somagen Diagnostics between September 29th, 2008 and October 2nd, 2008, the two VIP5 tissue processors are deemed to be operational. A full inspection was performed on the system on Wednesday, October 1st, 2008, where all mechanical and electrical aspects of the instrument were inspected and all found to be within and above manufacturer's specifications; thus ruling out instrument

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error as the cause for excessive xylene fumes. Somagen Diagnostics advises the laboratory to be diligent when performing charcoal and fume control water maintenance as these two are vital components of a fume management system on board the VIP5 tissue processor. Paraffin reservoirs in the oven will evaporate xylene which may be present in the paraffin into the surrounding air inside the oven. This air is then processed through the degassing cycle of the VIP5 tissue processor. In the degassing cycle, the air is passed through the charcoal filters to remove xylene molecules; however, if the charcoal filters are saturated with xylene, i.e. have not been changed as per the manufacturer's recommendations of once a month or every 20 processing runs, the fuel management system will not be operating at its full capacity. The fume control water operates by allowing formaldehyde and alcohol molecules to dissolve in the solution and therefore, the fume control water can also become saturated. The fume control water is recommended to be changed on a daily or every run basis. The laboratory is therefore

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advised to revise their SOP to reflect the charcoal and fume control of water maintenance for optimal fume management." And it's signed by Jamie Simpson. Now, gentlemen, and I appreciate you're not technicians for this machine, but based upon your experience if you did not change these charcoal filters on such a processor for six months, once for six months, beginning on month one and then for the next six months do not change it as you were supposed to, would that account for, from your perspective, what you observed or could it account for it?

MR. HEWLETT:

A. It certainly could

COFFEY, Q.C.:

Q. It could.

MR. PARKS:

A. It could, yes.

COFFEY, Q.C.:

Q. And your understanding, Mr. Parks, of the purpose of the charcoal filter is what?

MR. PARKS:

A. It removes the xylene from the air that's being pumped out of the oven area and it's a

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large--the fumes are drawn out by a vacuum pump and pumped through there.

COFFEY, Q.C.:

Q. So I take it, it just gets contaminated and -

MR. PARKS:

A. Yeah, the carbon absorbs organic molecules and you only have so many binding sites on a carbon and once they're full, it will no longer do its job.

COFFEY, Q.C.:

Q. If we could, please, I'd like to return, if I could to Exhibit P-3119? This is page 3 of your report, I take it the report then was prepared by yourselves after leaving St. John's on September 30th.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. You would have gathered the data and started, I presume while you were here, but the final report--and it's a joint effort by yourselves.

MR. PARKS:

A. Yes, it was.

COFFEY, Q.C.:

Q. Here on page 3 in relation to fixation and it

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reads "Observation of the specimen receiving area, specimen triage and the grossing of the specimens, along with the review of documentation leads us to believe that the issue of fixation has been satisfactorily addressed. The fixation of all specimens is now 24 hours or long, with the exception of a few 'Rush' specimens. The PAs are preparing large specimens in such a manner as to optimize fixation. Chance observation by one of us"--that was Mr. Hewlett--"at the St. Clare's site after receipt and handling of a fresh breast localization specimen, provided the opportunity to confirm appropriate handling of such a specimen in accordance with the document." And that is the policies and procedures manual we have here as Exhibit P-2157, I believe, Commissioner. It's here PRC-(PAT 218, v2) in the new policy and procedure manual. A similar chance observation of an inter-operative consultation (Quick section) provided the opportunity to review the handling of this type of specimen in the frozen section lab in the operating room. It was noted that a refrigerator was available in

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the frozen section room to accommodate the fresh tissue in case of any delay in the pathologist's arrival. The procurement time, date and time received in the lab, time in the fixative for fresh specimens, date and time of grossing are all recorded on the requisition. This information is dictated into the gross description which provides documentation and is available to users of the tissue block for all future studies. In addition, the date and time of tissue processing are subsequently documented and ultimately used to determine total fixation time. This is in compliance with existing Canadian Consensus Guidelines for HER2/neu testing and the soon to be published guidelines by the Ad Hoc committee on ER testing." Now gentlemen, having read that out I have a couple of questions. One is to you, Mr. Hewlett, this ad hoc committee that is referred to, that's the committee you're a part of?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And they're about to publish guidelines in

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relation to ER/PR, I take it.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. Gentlemen, here there's a reference to your ability to observe the dissection of the breadloafing of tissue.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And you found it appropriate. Did you have any--and I appreciate you did see the breast tissue, in your own case, Mr. Hewlett, did you have any opportunity to observe or make any inquiries concerning how or what process or procedure is in place for transporting tissue from an OR to the lab that is not breast tissue, like non-breast tissue? For example, a kidney, I'll just pick a kidney.

MR. HEWLETT:

A. Not to observe.

COFFEY, Q.C.:

Q. But did you have any understanding about -

MR. HEWLETT:

A. Some material was already received and that

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was date and time stamped, as it should be. What happened prior to that, I have no idea.

COFFEY, Q.C.:

Q. If, and we have, the Commissioner has heard a witness, Marie Tracey, who was the peri-operative director for the two St. John's hospitals you were in, she has testified that certainly breast tissue is in effect very quickly moved from the OR location through a porter system, down to the lab and special arrangements are made if it's late in the day and the normal porter system doesn't pick it up, that it's transported to the lab regardless by the end of the day. But that's not true of any other tissue, other tissue, if it makes the normal porter runs, it gets down, but if it doesn't make a normal porter run, it spends, it stays overnight, not breadloafed in formalin in the OR or spends the weekend there and goes down on Monday. Now do you have any--and I'll ask you, Mr. Hewlett, do you have any observations about any potential problems that that might cause?

MR. HEWLETT:

A. Oh absolutely.

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COFFEY, Q.C.:

Q. And I suppose it's a way of asking, is there anything peculiar about breast tissue compared to other types of tissue in relation to the need to handle it in a particular way in terms of fixation? Compared to breast, for example, compared to liver or -

MR. HEWLETT:

A. No -

MR. SIMMONS:

Q. Excuse me, I think Ms. Tracey's evidence was that there were some other specific types of tissue transported down in the same way as breast -

COFFEY, Q.C.:

Q. Oh no, yes.

MR. SIMMONS:

Q. It's not that -

COFFEY, Q.C.:

Q. No, no, she said no pathology specimens were. She said other specimens, biochemistry and there were a whole bunch of others, they're all spelled out, but other pathology specimens and I stand to be corrected, Mr. Simmons, but I think all other pathology specimens, liver,

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I don't know, a piece of muscle, whatever.
THE COMMISSIONER:
Q. Your question relates to whether or not the treatment of pathology specimens which are suggested in respect of breast, would be any different for other kinds of pathology found specimens.
COFFEY, Q.C.:
Q. Yes, that's correct.
MR. HEWLETT:
A. My comment about that would be our colleagues in the biochemistry laboratories and other laboratories have had sample procurement procedures for years and, you know, if you have a sample of blood taken, they will simply reject it if it doesn't meet the sample requirement procedure. In histology, we cannot reject samples because we can't go back and reobtain them in many cases, so we don't have the same kind of outright rejection policy. But blood is a tissue, the same as the tissue that--the most solid tissues that we dealt with and the same conditions apply. For all specimens, they need to be handled on a timely basis. If the sample is small

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enough, it can simply be placed into fixative. I would place the outer limit in terms of thickness maximum dimension of thickness, one centimetre, I would like to see it less -
COFFEY, Q.C.:
Q. That you could kind of just take, put in formalin and -
MR. HEWLETT:
A. And forget about it.
COFFEY, Q.C.:
Q. And leave it there, whether it was overnight or over the weekend, as long as it's fully -
MR. HEWLETT:
A. For reasons I can either explain to you now or in the presentation -
COFFEY, Q.C.:
Q. Well go through the presentation in terms of that, but for reasons it will be explained later today.
MR. HEWLETT:
A. Yes, yes.
COFFEY, Q.C.:
Q. Go ahead. Anything bigger, you would want to deal with differently.
MR. HEWLETT:

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A. Absolutely.
COFFEY, Q.C.:
Q. And how should it be dealt with, anything bigger?
MR. HEWLETT:
A. It needs to be opened, sliced, breadloafed, call it what you will and so that the surfaces are now exposed to formaldehyde so appropriate penetration can take place and that believe it or not has absolutely nothing to do with fixation time. Penetration is one thing; fixation is something completely different, but they are connected. One can't fix until the material has penetrated.
COFFEY, Q.C.:
Q. And I'll be asking you to elaborate on that later in the day.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. But in terms of any pathology specimen, unless it's a centimetre or less in size, in which case it should go into formalin in the OR and whether it gets down that day or the next, as long as it's covered well enough -

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MR. HEWLETT:
A. There may be other issues, for example, some samples if one wishes to look for the presence of uric acid crystals in gout, we certainly don't want those placed into formalin, they have to go into alcohol. So there are special conditions for some examinations. Electromicroscopy, flowcytometry samples, all that sort of thing and the best way to handle that is to have the pathologist get to the fresh tissue as quickly as possible.
COFFEY, Q.C.:
Q. Yes, but for anything that, any pathology specimens that are intended to be formalin fixed -
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. They should be handled in a way you take it you observed the breast tissue being handled at St. Clare's?
MR. HEWLETT:
A. Exactly.
COFFEY, Q.C.:
Q. In the process, move it along and make sure it

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gets breadloafed.
MR. HEWLETT:
A. Yeah, within a certain timeframe. It's okay to dump a large specimen into an adequate volume of fixative and transport, but it's a question of total, sorry, ischemic time. The moment blood supply is cut off, the tissue starts to degenerate and for estrogen receptors, we have an ideal time limit of about 15 minutes, 30 minutes max. If we can cool that tissue down, we can extend that time up to maybe an hour, perhaps even as much as two hours.
COFFEY, Q.C.:
Q. Before you put it into formalin.
MR. HEWLETT:
A. Yeah, yeah.
COFFEY, Q.C.:
Q. But even when it is in formalin in a large sample size, I take it that it's just not enough to put it in formalin, you have to as well get it breadloafed properly. And in terms of that, Mr. Hewlett, and I'll just use the example of a kidney, somebody had a kidney taken out in the OR, what would the potential

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affect be if the kidney is to be preserved with formalin, that's the aim, but it was just simply left in a container of formalin overnight or over the weekend in the OR, what would -
MR. HEWLETT:
A. The outside few cells will fix, the inside will still be raw and degenerating. The speed of the generation depends somewhat on the tissue, so and basically on a glandular component, so if we took a sample of, say, pancreas which is full of digestive enzymes, that would self destruct very rapidly; whereas if we took a piece of skin, those cells may be viable for quite a number of hours without damage, so it depends on the tissue somewhat.
COFFEY, Q.C.:
Q. And Mr. Hewlett in relation to this matter, for all pathology specimens, tissue specimens, I take it that if they're going to be, it's intended to fix them with formalin and the subsequently have IHC tests done of whatever sort on them, that it's important that they be fixed properly, whether or not it's breast or anything else for that matter.

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MR. HEWLETT:
A. Absolutely. The fixation, you've probably heard this many times, but fixation is the entire key to histological techniques. If the material is not appropriately fixed and well fixed, then everything else can fail. It's so crucial that it's hard to over emphasize.
COFFEY, Q.C.:
Q. Mr. Hewlett, because you did have the opportunity to observe and in particular the breast tissue sample you saw dealt with at St. Clare's and bearing in mind your observations about the transport across St. John's, okay?
MR. HEWLETT:
A. Uh-hm.
COFFEY, Q.C.:
Q. But if all pathology specimens that were intended ultimately to be dealt with by way of being fixed in formalin and embedded in paraffin blocks were to be dealt with as breast tissue was, would you think that that's an appropriate -
MR. HEWLETT:
A. Yes, I do.
COFFEY, Q.C.:

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Q. So if they could do for other things what they're doing for breast tissue, that would be a better state of affairs.
MR. HEWLETT:
A. I do realize it depends so much on the nature of the examination required. One could argue, for instance, if you have a ruptured appendix, then it's maybe not so important to have a really good preservation, but approximately one in ten thousand ruptured appendices are due to presence of a particular kind of tumour and that requires immunohistochemistry. So one never knows and we're in the era of targeted therapies, what we currently have is just the beginning. There are 20 or 30 more about to come on stream. Most of those therapies will require some form of immunohistochemistry most likely to determine suitability of the candidate for the therapy. So it would be prudent to have all your material appropriately fixed and in storage because one never knows what's coming down the pipe. ER is a good case in point, as is HER2, CD117 and so on. These are currently existing markers that are crucial. I think there's a

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responsibility knowing this that all material coming into a histology lab should be appropriately fixed because we don't know what we may be asked to do on that material next week or two months from now or two years from now and the source of that material is currently in the pathology files.

COFFEY, Q.C.:

Q. Here under fixation in italics is written "The 10 percent buffered formalin currently in use is a purchased produce and the pH and formalin concentration is neither being checked nor documented by the staff." Now what lead you to believe that?

MR. PARKS:

A. What led us to believe that?

COFFEY, Q.C.:

Q. Yes.

MR. PARKS:

A. We inquired, I did at the Health Sciences Centre and Bryan did at the St. Clare's. And I noticed that the jugs of formalin were boxes, were just stacked up and I inquired about the use of formalin and the pH they were using and the concentration, if it had ever

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been teetered to determine the concentration and they had not.

COFFEY, Q.C.:

Q. And it continues on, "The purchased fixative formulation is not the conventional phosphate buffered formalin used and the pH is not stated on the product label. The constituents of the solution listed on the MSDS sheet supplied by the manufacturer are not the same as those listed in a conventional Sorenson's phosphate formalin buffer and nowhere is the final pH indicated. An on-site test of the fixative in use indicated a pH of 6.86, which is below the optimal range." Who conducted the -

MR. PARKS:

A. That was Bryan who conducted that at the St. Clare's.

MR. HEWLETT:

A. We actually had them check it, pull a sample from the container and check.

COFFEY, Q.C.:

Q. And I'm just going to finish this and then ask you a question. "The Eastern Health group and potentially a Provincial purchase of large

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volumes of commercial formalin should allow for the specification of the formulation and pH by the purchaser. Requesting a conventional phosphate buffer with a pH of 7.2-7.4 would provide a product that is compliant with all current immunohistochemical antibodies and guidelines." Now, Mr. Hewlett, you checked it at the time, I take it this would be, was this a Friday, was that the Friday that -

MR. HEWLETT:

A. Yes, at St. Clare's, yes, and I rechecked when I was at the Health Sciences.

COFFEY, Q.C.:

Q. And what did you find? It was 6.86 at both or -

MR. HEWLETT:

A. I'm sorry, I didn't recheck the pH at the Health Sciences. I checked the container and the labelling.

COFFEY, Q.C.:

Q. Labelling.

MR. HEWLETT:

A. It's the same product, they are group purchasing and subsequently, as you will see,

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I checked the product in other centres and it's all the same product.

COFFEY, Q.C.:

Q. What's the effect of any, or potential effects of having a pH of 6.86 as opposed to what's specified here as 7.2 to 7.4?

MR. HEWLETT:

A. The amount of fixation will be somewhat different.

COFFEY, Q.C.:

Q. And why is that, can you -

MR. HEWLETT:

A. Very briefly the actions of formaldehyde as a fixative are affected by the pH and concentration and by the various buffer salts incorporated and sometimes in unpredictable ways a more efficient fixation occurs from about pH 7 to 7.6. Physiologic pH is 7.4 approximately. You get improvements in fixation quality actually up to pH 8, but at pH 8, there's some damage due to the pH occurring to the tissues, so we need to back away from that a little. So the commonly accepted range is actually 7 neutral to 7.4. When using fixatives, it's very common when

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placing the tissue into the fixative, there will be a pH drop of about .2.

COFFEY, Q.C.:

Q. Okay.

MR. HEWLETT:

A. Due to the acidity of the tissue itself, the more blood contained in the tissue, the more the drop will occur and so if you are using a pH 7.2 buffer, it could drop to pH 7 which is considered neutral buffer formaldehyde.

COFFEY, Q.C.:

Q. Yes.

MR. HEWLETT:

A. And that's the beginning of the appropriate range.

COFFEY, Q.C.:

Q. And in this case when you checked it at St. Clare's, were you checking used formalin or you're checking the fresh?

MR. HEWLETT:

A. No, straight out of the container.

COFFEY, Q.C.:

Q. Straight, 6.86, so if there's this .2 drop, it would go down to about 6.6, roughly. I take it that's what is expected?

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MR. HEWLETT:

A. Yeah, interestingly, I asked the people at St. Clare's if they knew what the pH was supposed to be and we pulled out the MSDS sheet and checked and so on and there's no mention. And so she actually went away and found the manufacturer and said what is the pH of this product and they said, oh, we'll have to get back to you and they did. And they indicated that the range was 6.8 to 7, this is from the manufacturer. When we did this at another location, they also phoned the manufacturer and were told 6.9 to 7.1. I'm not sure which I believe, but -

COFFEY, Q.C.:

Q. And I take it from your perspective, it should be on the label, in any case?

MR. HEWLETT:

A. It should be on the label in any case, and it should be on the MSDS sheet, and it should be of the appropriate range. It doesn't say anywhere on the label this is neutral buffered formalin or formaldehyde. It should. It just says "buffered". So I looked at the constituents of the buffer and they're not

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traditional buffer phosphate salt that is normally used and recommended in most of the textbooks.

THE COMMISSIONER:

Q. Just because it's running through my head, perhaps Mr. Parks, you're the better one to ask, do you - I assume you buy your -

COFFEY, Q.C.:

Q. Formalin.

THE COMMISSIONER:

Q. Formalin. Thank you.

MR. PARKS:

A. Actually, no -

THE COMMISSIONER:

Q. Or do you mix it?

MR. PARKS:

A. Actually, we make our own.

THE COMMISSIONER:

Q. You mix it yourselves, okay.

MR. PARKS:

A. We buy a concentrate. We use the monobasic and diabasic phosphate salts, which are weighed out, and then after the stuff is made, we do a tedder of the jug of formalin before it goes into use to make sure that the

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concentration is in the correct range.

THE COMMISSIONER:

Q. And in the labs in which you work?

MR. HEWLETT:

A. Some of the labs purchase, and it's a traditional Sorenson's phosphate buffer, it's pH 72 nominally. In the actual centre where I work we made our own in huge vats, weighed off the phosphate salts and dissolved them, made up the buffer, put samples to check pH and the osmolarity, that's the concentration, as it were, and before adding formaldehyde, which changes the osmolarity, and then again afterwards and it was checked for pH concentrations and so on.

THE COMMISSIONER:

Q. For those who purchase, would you recommend accepting the manufacturer's word on the point or would you - in our labs, would you check, in any event?

MR. HEWLETT:

A. It's prudent, and actually in Ontario, part of the licensing regulations that you confirm purchased product as to specifications.

COFFEY, Q.C.:

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Q. And that, I take it, is when it first comes in?
MR. HEWLETT:
A. When it first comes in.
COFFEY, Q.C.:
Q. And how about after -
MR. HEWLETT:
A. Just before putting it into use.
COFFEY, Q.C.:
Q. How about afterwards? If you have formalin sitting in a premixed sealed container, I don't know, for a month or two or three in a warehouse, or it's opened and then sitting unused for a month or two?
MR. HEWLETT:
A. It would be prudent to check it again. Most hospital labs are going through a fair amount of this stuff and so it's best before date is way in excess of when you actually run out. So every batch would be checked for pH, and hopefully for concentration before being placed into use, and if it was going into storage - I'm thinking in terms, Commissioner, of pre-filling specimen containers, delivering them to the OR, they should be date stamped,

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to make sure they rotate the product so, you know, that don't sit in the back like -
THE COMMISSIONER:
Q. Like in the supermarket shelf.
MR. HEWLETT:
A. Exactly.
THE COMMISSIONER:
Q. The product at the back gets moved forward.
MR. HEWLETT:
A. Yes, exactly.
COFFEY, Q.C.:
Q. Commissioner, I'm going to move on to the processing on page four.
THE COMMISSIONER:
Q. Uh-hm. Do you want to take the break before we do that?
COFFEY, Q.C.:
Q. If we could, please. Thank you.
THE COMMISSIONER:
Q. All right, we'll take fifteen minutes.
(BREAK)
THE COMMISSIONER:
Q. Mr. Coffey.
COFFEY, Q.C.:
Q. Thank you, Commissioner. Looking at page four

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of P-3119 in the heading processing, you've written, "There is strong evidence that an ongoing problem exists with the processing of the tissue blocks. New tissue processors had been installed approximately eight months ago. A random review of blocks and the storage slides between the years 1998 and 2007 consistently found blocks that showed evidence of inadequate processing. We randomly pulled several paraffin blocks containing large pieces of tissue from the storage drawers and found poorly processed tissue within a few blocks of the initial sampling in a drawer. The tissue in the blocks examined was either retracted from the surface and dry or was oily to the touch. This is indicative of tissue that was insufficiently dehydrated, cleared, or infiltrated respectively. We did not find blocks containing smaller pieces of tissue that showed similar inadequate processing. This would indicate that the large tissue blocks were likely too thick to be adequately processed by the routine processing schedule". I take it, Mr. Hewlett, that refers to the situation where you went back before the

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current processors were in use?
MR. HEWLETT:
A. Exactly, yes.
COFFEY, Q.C.:
Q. And it goes on, "Another artifact observed in some of the blocks was a very evident interface line separating the tissue and the surrounding supporting paraffin. This can occur if the tissue is allowed to cool or is drained of molten paraffin before being placed in the mould during the embedding process". I'm going to go then, if I could, to the next page. This is the same section, last paragraph reads, "On two separate occasions, we observed the practice of removing racks of cassettes from the tissue processors and placing them into heated empty holding wells on the embedding centre. Embedding of these cassettes took up to two hours and during this time the blocks cooled and liquid paraffin had drained from the tissues. We recommend these holding wells be filled with molten paraffin to ensure that the tissues remain completely infiltrated until embedded. This will maintain the liquid paraffin phase at the

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outside tissue surface during embedding and will also prevent separation interfaces forming between tissue and supporting paraffin". Mr. Parks, in particular, I think you spoke about that?

MR. PARKS:

A. Yes, I did.

COFFEY, Q.C.:

Q. What is the effect, Mr. Parks, of that condition where you get this separation, as you said? Like, down the road, as you then utilize the blocks, what's the effect?

MR. PARKS:

A. Well, one of the effects is when you go to cut the tissue, the tissue isn't supported by the wax around it, so you can get uneven in the cutting of the tissue. Also when it goes onto the water bath, the tissue tends to separate from the wax and it - the surface of it, there can be damage as it pulls away on the water bath and stuff. It is not a real - it doesn't have a lot of long term - you can easily correct this just by taking these back and putting them into wax, but it does create problems when you are cutting.

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COFFEY, Q.C.:

Q. For handling, I take it?

MR. PARKS:

A. For handling of it, exactly, orientation of this thing on the slides because it is a interface - especially with tougher tissue, you do need the tissue being - the paraffin around the tissue supports it in the cutting, and gives you an adequate thin section that you are requiring for your subsequent studies, even sectioning of the tissue.

MR. HEWLETT:

A. If I may add, if the tissue is particularly hard and small, during the cutting process, it can cause the tissue to actually shell out of the block, and then there's, you know, this danger of loss of specimen at that point.

COFFEY, Q.C.:

Q. Shell out in the sense of like literally come out of the block?

MR. HEWLETT:

A. It'll literally pop out of the block because it's not held in place. The paraffin should be continuous through and through.

COFFEY, Q.C.:

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Q. Through the whole block and tissue?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. With continuous interface.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And here you continue on page four, "A random review of blocks in the storage files for the last six months also consistently found some blocks showing evidence of inadequate processing. These also were blocks containing large pieces of tissue. Again we would initially tend to blame tissue thickness as the culprit". I take it that was at the time in terms of your thought processes, and then you go on to say, "Examination of the section cutting sheets of the previous day indicated a few samples classed as fatty tissue, difficult to cut. We also examined these blocks and noted that they were of large tissues and showed evidence of inadequate processing. Observation of the PAs during grossing of large specimens showed the appropriate

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selection of tissue thickness being placed in cassettes. These cassettes were followed and placed on one of the new tissue processors for overnight processing. We observed embedding of these blocks the next morning and their subsequent sectioning. These sections were also difficult to cut and blocks felt oily to the touch. These large tissues were of appropriate thickness. As this issue has been addressed by the PAs and is no longer a contributing factor to inadequate processing". So I take it, gentlemen, that in terms of the years between '98 and '07, the sizing of the tissues at times made the process problematic. In the past year, the ones you looked at, it's not the sizing issue, it's the processing issue?

MR. HEWLETT:

A. It's the processing issues, yes.

COFFEY, Q.C.:

Q. And it goes on to say then, "A review of the processing schedule used on each of the processors showed that there's inadequate number of graded alcohols in the dehydration sequence. We recommend that the processing

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schedule be modified to increase the number of graded alcohols in the sequence and to make use of the technology available on this instrument in order to improve the overall efficiency of the process. See Appendix I". I'll take you to that. This is Appendix I, and it's routine overnight process schedule, and stations 1 to 14 are filled out, and biopsy program, stations 1 to 14. Mr. Hewlett, can you tell us, please, what this is about, this aspect of the matter?

MR. HEWLETT:

A. This is the schedule of reagents and times set upon the processing machine. So once the cassettes are loaded, they will be in station 1, commence start with the machine, it will pump in in this case formalin. It will allow that to remain for 60 minutes. We have - we are suggesting an increased temperature. The existing schedule has ambient room temperature. We are suggesting they increase the temperature because diffusion of reagents occurs more rapidly at higher temperatures, and that will increase the efficiency of the diffusion in the reagent through the tissue.

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As part of that, you see the little column marked PV. On this particular instrument, there is an alternating pressure vacuum cycle. A portion of the fluid is withdrawn from the retort and then pumped back in under positive pressure. I think that takes about three minutes for that cycle, and there is also a mixing cycle and we changed it from slow, which is the current setting, to fast. When you have a turbulent flow, you again get a more efficient exchange of reagents.

COFFEY, Q.C.:

Q. There's more fluid flow?

MR. HEWLETT:

A. More fluid flow, yeah.

COFFEY, Q.C.:

Q. Across the surface, and, therefore, more exposure?

MR. HEWLETT:

A. Exactly.

COFFEY, Q.C.:

Q. And if -

MR. HEWLETT:

A. And shortening of the effective time. While we're not changing the time too much, we're now being sure that tissues which are slightly thicker will have long enough in each reagent for complete diffusion and penetration to occur.

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COFFEY, Q.C.:

Q. Here's there's a reference in the text itself to recommend the processing schedule be modified to increase the number of graded alcohols in the sequence. Why was that thought appropriate?

MR. HEWLETT:

A. Because of the jump in grades of alcohol. So if one starts at 70 percent alcohol and then jumps to 100 percent, the best way I can put this is to imagine how you would feel if somebody dropped you into a bath of ice cold water, it's a bit of a shock on the system, and the effect of that sudden jump in a dehydrating sequence is to cause the proteins in the tissue to literally shrink in a shocked manner, and that is something we don't wish to occur.

COFFEY, Q.C.:

Q. So you would increase the number of graded alcohols?

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MR. HEWLETT:

A. Yes, so we're going 70, and then a 10 percent increase in concentration, and then a jump to 95, and then finally the absolute.

COFFEY, Q.C.:

Q. What was actually being used at the time when you were there, do you recall?

MR. PARKS:

A. It was going from 70 to 80, and then from 80 to 100, which is very, very big shock on tissue, and I refer to that as you want to be gentle, and the smaller the jump you make, the more gentle it is on the tissue. So they were making a large jump from 80 to 100, which is really quite a shock on your tissue.

MR. HEWLETT:

A. And not only that, remember the idea is to remove the water. Well, we need less than about - certainly less than 2 percent water content before it goes into xylene, otherwise they won't mix. If you go from 80 percent alcohol into 100 percent, there is a carry over of 20 percent water, and you've only got three changes to dilute that water out, so to speak, and you can do calculations to

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determine how many changes do you need.
COFFEY, Q.C.:
Q. So - and this is, I take it, the suggestion?
MR. HEWLETT:
A. This is a suggestion we're making.
COFFEY, Q.C.:
Q. A different approach.
MR. HEWLETT:
A. It's not written in stone - if they wish to extend their times. I certainly wouldn't reduce them much.
MR. PARKS:
A. We did some -
MR. HEWLETT:
A. Added temperature.
MR. PARKS:
A. Sorry.
COFFEY, Q.C.:
Q. Go ahead, I'm sorry.
MR. PARKS:
A. We had also done on our flight down here some calculations of the times it would take for the volumes of tissue for what we were processing, and we - remember we looked at that as to what would be the minimum times and

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then we also added the temperature to increase the efficiency of the machine and this here allows - as Bryan had alluded to earlier, pathology had - programs had been shortened to get the work out on time, and this makes use of all the efficiencies available to provide a program that would definitely process all of your tissue very well by finish time at 5:30 in the morning.
MR. HEWLETT:
A. Provided it's not too thick.
MR. PARKS:
A. Yes.
COFFEY, Q.C.:
Q. Provided it's below the maximum thickness?
MR. PARKS:
A. Yes.
MR. HEWLETT:
A. Yeah.
COFFEY, Q.C.:
Q. And if you're going to go with these, in terms of your times, in order to finish at 5:30, then it's your suggestion that these--is a suggested usage of graded alcohols?
MR. HEWLETT:

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A. Yes.
COFFEY, Q.C.:
Q. In this order, and these are suggested temperatures, not necessarily the ones that they were utilizing at the time?
MR. HEWLETT:
A. Actually, the temperatures, they're using no temperature all the way through until wax. Obviously there's a temperature in wax to keep it molten, and that is the temperature of this particular wax. We've added 37 Celsius to all the other reagents for a couple of reasons.
COFFEY, Q.C.:
Q. If I could, Mr. Hewlett, just before you go on, if I could just go back to page four, because I wanted to ask you, and I suspect you're about to get into it, you do conclude that paragraph by saying "and to make use of the technology available on this instrument in order to improve the overall efficiency of the process."
MR. HEWLETT:
A. That's exactly it, raise the temperature of the process and increase the mixing rate.
COFFEY, Q.C.:

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Q. So that's something that can be done by adjusting -
MR. HEWLETT:
A. Anybody. It's built into the programming. You can adjust that. The original program was, I believe, set by the factory technician, as is commonly the case, and I personally would not allow that to happen in my laboratory and I don't think you would, would you, Bill?
MR. PARKS:
A. No.
COFFEY, Q.C.:
Q. So here, this temperature, what you saw when you first went there, the paraffin was certainly--there was a certain fixed temperature.
MR. HEWLETT:
A. There has to be.
COFFEY, Q.C.:
Q. Programmed, because of the melting point of paraffin?
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:

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Q. But as best you could tell, the temperatures themselves otherwise, in these earlier stations, which is really one through ten -
MR. HEWLETT:
A. Temperature was off.
COFFEY, Q.C.:
Q. Off.
MR. PARKS:
A. It was called the ambient stage, and on these machines ambient is room temperature.
MR. HEWLETT:
A. That's room temperature.
COFFEY, Q.C.:
Q. Room temperature, and so you're suggesting that they run at 37? Set the machine so stages one--stations one through ten -
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. - the temperature inside the machine, in respect of these solutions, is at 37?
MR. PARKS:
A. Correct.
MR. HEWLETT:
A. And if I may add, at this point, although it's

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possible to go higher, up to 45, and that certainly works and would give you a few more efficiencies, we've deliberately kept it to 37 in view of the guidelines about to be published which state you should not exceed 37.
COFFEY, Q.C.:
Q. These ad hoc committee guidelines.
MR. HEWLETT:
A. Yes, exactly.
COFFEY, Q.C.:
Q. Okay, and with that in mind, and as well, I take it, you've indicated that the machine allows for adjustment of the fluid flow rates?
MR. PARKS:
A. Yes.
COFFEY, Q.C.:
Q. And to set it to fast.
MR. PARKS:
A. On this machine here, the fluid flow is actually removing the solution from the chamber and pumping it back in over top of it. In the fast, it does it every 12 minutes. In the slow, I believe it's every 20 minutes. So we--they were only on the slow, which with

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large tissue, more turbulence flowing over top of it provides much better contact.
MR. HEWLETT:
A. Mixing and contact, yeah.
COFFEY, Q.C.:
Q. Okay, and was there anything else further in respect of these--I take it what applies--this is routine overnight process schedule for Appendix 1, and there's a different one for the biopsy program?
MR. HEWLETT:
A. They had another program on there for biopsies and rush specimens and so on and these are smaller yet pieces.
COFFEY, Q.C.:
Q. And the times are particular different -
MR. HEWLETT:
A. And the times are shortened down to allow for that.
COFFEY, Q.C.:
Q. Okay, and anything else of significance in relation to these, gentlemen? If we could then go to page five. You've written, "we observed that the racks loaded in the processors had the organized cassettes packed

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tightly together. A further improvement in process efficiency could be obtained by reducing the number of cassettes in each compartment of the rack from ten to eight. The staff will still be able to maintain the order of cassettes in the rack, which is an excellent QC practice, by providing more space between individual cassettes. This will help to ensure superior reagent flow around the tissue." And you've spoken to that in particular, Mr. Hewlett.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. You go on "further hands-on review of both instruments revealed xylene contamination of all paraffin baths. This is far in excess of normal. Only the initial paraffin bath should have any significant xylene content following a process run. Documentation of the schedule reagent changes was available and indicated that paraffin on both instruments had been changed within the specified time limits. If these changes had in fact occurred as indicated on the documentation sheet, then

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this constitutes an unusual event. We strongly suggest that these new instruments have preventative maintenance performed by the manufacturer, in particular to check that the instruments paraffin degassing function is operating properly and that excessive reagent carryover is not occurring. In the meantime, the immediate action of replacing the contents of all paraffin baths on both instruments with fresh paraffin is urgently recommended. See Appendix 2.

On Monday, we observed the technician changing all reagents on a processor. We checked the paraffin baths for odour and viscosity before the processor was started that evening and found them to be clean and free of xylene. On Tuesday morning, we inspected the paraffin baths after the processing run and found them to be highly contaminated. This would point to a instrument problem." And you've been telling us about what happened, and I've showed you what the technician found afterward when he came in.

MR. PARKS:

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A. Yes.

COFFEY, Q.C.:

Q. One thing I wanted to ask you about, actually, I'll take you to Appendix 2 first, and then I have a question. Appendix 2 reads, "the ethical issue of knowing that further patient specimens were to be run on the processors with the contaminated paraffin could be potentially compromised prompted us to contact B. Coffey on the 28th of September. We discussed our concerns with Mr. Coffey and asked if we would be able to recommend to laboratory management that the processing reagents would be changed on Monday before any other tissue was processed. We were advised to proceed to ensure that these tissue samples were not compromised." And that's the conversation you've indicated you had with me on that weekend.

Gentlemen, what I wanted to ask you about in terms of this whole issue about smelling xylene, okay, did you ask anybody why they hadn't noticed it? I take it it was readily apparent to yourselves?

MR. HEWLETT:

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A. Oh yes. It's an insidious thing. If you work in that environment, you cease to smell it. You cease to notice it.

MR. PARKS:

A. And I have the same thing with guests that come into my lab, and I should say that when I walked into the hallway of pathology here, and I work in histology, I'm in my lab six-seven hours a day, I noticed a much higher odour in the lab than I do in my own, which people who don't work in labs notice somewhat of an odour in mine. But if they've been in that the whole time, your senses to it become somewhat deadened and because of the work flow through there, the fumes are all over that whole area.

COFFEY, Q.C.:

Q. What in particular though--because the xylene caught your attention when you were at the processor. Did you ask anybody about well, is it--I take it that's not a normal thing, not that common?

MR. PARKS:

A. Not to that extent.

MR. HEWLETT:

A. Not to that extent, no.

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COFFEY, Q.C.:

Q. Did you ask anybody why they didn't notice it or didn't remark upon it?

MR. PARKS:

A. Well, the only person with the position -

MR. HEWLETT:

A. Only the PA.

MR. PARKS:

A. The PA commented to us that she did notice that the xylene fumes were strong in that room and she'd often noticed that, but the technician who runs the machine -

MR. HEWLETT:

A. Can't smell.

MR. PARKS:

A. - he can't smell, so he did not notice that.

COFFEY, Q.C.:

Q. And I take it the significance of it, apparently, hadn't occurred--potential significance hadn't occurred to him?

MR. PARKS:

A. No, I don't think it had been--again, it comes to the disconnect of information. People should have been noticing that and they weren't acting on it.

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COFFEY, Q.C.:
Q. And if it was due to the failure to change the filters once a month, I take it over time the problem with not changing the filters would progress over time?
MR. PARKS:
A. It would get worse because the carbon becomes totally--cannot take another molecule of xylene, so it would not be working properly at all.
COFFEY, Q.C.:
Q. So it would gradually build up.
MR. PARKS:
A. It would.
MR. HEWLETT:
A. But also the fumes in the room would increase.
MR. PARKS:
A. Yes.
MR. HEWLETT:
A. Because they're not being absorbed by the charcoal filter. I mean, the air goes through the filter and is pumped back into the room.
COFFEY, Q.C.:
Q. Page five, to continue. You've noted here, at the bottom of the page, "it is fortunate that

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the tissues have been optimally fixed for some time, according to the records. This fact mitigates any potential tissue compromise due to inadequate processing on these instruments" and you've referred to that, and that relates to the damage to the cellular structure of the tissues, I take it?
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. Until the technician was in, the problem caused by the consistency or lack of consistency of the blocks remained?
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. Okay. It goes on, "on two separate occasions, we've"--and we've talked about the cassettes then. If we could go then, please, to Manuals and Documentation, which is on the next page, page six. You've written "we spent considerable time reviewing the new policy and procedure manual. The manual is a work currently in progress. Although an incomplete document, the Eastern Health staff is to be

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commended on their accomplishment to date, in spite of maintaining high workloads and without significant additional resources. The manual is very well written. The new methods are detailed, concise and easy to understand. The completed sections are certainly equivalent, and in some cases, superior to accredited laboratories in other jurisdictions." I take it you're both of that opinion?
MR. PARKS:
A. Definitely.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. It goes on "there is a evidence of the use of the new procedures at the St. Clare's Mercy site. The staff at this site is aware of the new manual and have been reading and signing off on relevant sections. They have also demonstrated their knowledge through application in several situations during our visits to the site. Unfortunately, the majority of bench staff at the Health Sciences Centre site appears to be uninformed of the

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existence of this new document and staff in-service education session regarding reading and sign off of the new relevant manual sections is strongly suggested." And you've spoken about that in particular, Mr. Parks. "There is considerable evidence of thorough documentation throughout the work processes at both sites," and you again, Mr. Parks, have spoke of that, as did Mr. Hewlett.
And then you've written "the specimen worksheet produced at the beginning of the histology process is an excellent method of information flow and accompanies each specimen as it passes through the workstations of the laboratory. Information that may be necessary in subsequent processes is added at each step. From the specimen sheet, it is possible to determine when it was processed, what processor was used, any problems in embedding and what staining run it was on. There is a large quantity of information available on each specimen that passes through the lab, and this is very commendable, but not all the information is together. Unfortunately, this worksheet bypasses the microtomy bench and

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comments about the specimen at this point are kept in a separate binder." Mr. Parks, you mentioned that. I take it you felt they should be--the paper should continue on?

MR. PARKS:

A. They should be all tied together.

COFFEY, Q.C.:

Q. All tied together. Is there any reason why it couldn't be, that you observed?

MR. PARKS:

A. It could be, especially the way they organize their blocks and slides and distribute them to the microtomy technologists. The sheet could easily follow along, because they do things in batches and they keep things very organized. So it could easily go to that spot and the notes could be written right on at that point. It's a little more messy area of work because there's wax and stuff, and maybe they decided not to, but it definitely could follow, and it would be--it would complete that document very well.

MR. HEWLETT:

A. If I may, the one concern they had about this was it would require duplicating the document

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because the next station, staining, they require that document to prepare their slide labels and all those other things. So you know, there's a logistical thing there, but we still both believe it should be kept together.

COFFEY, Q.C.:

Q. That or a copy, a photocopy of some sort.

MR. PARKS:

A. The thing could still carry on. I think that they wouldn't even have to photocopy it. It could just follow the slides. When they bring the slides and the blocks out for cutting, because the slides are prelabelled, they could easily have that, the paper, with it at that point. It bypasses and goes on and it could easily catch up when you take your slides over for cutting. I still think that it would be a very minor change and I don't see duplicating that paper necessary. I think all information should always be contained in a single document, so there's not crisscrossing of papers and that's where quality and total quality management comes together, is when everything is available.

COFFEY, Q.C.:

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Q. And it could be addressed?

MR. PARKS:

A. Oh, it definitely can be addressed.

COFFEY, Q.C.:

Q. And it goes on "there are sign-off sheets at many of the workstations assigning ownership and responsibility for the task. Where possible, the specific case numbers are also listed. Corrective action record sheets are in use in the block sorting area and in special stains. One of the most important QC checks in histology occurs at the H & E staining bench. Slides and blocks should be brought together for comparison after staining to ensure that a complete section of the correct tissue was on the slide. This QC check is not being performed or documented at this time." Mr. Parks, what should be going on there?

MR. PARKS:

A. When you finish your staining and before the slides leave the lab -

COFFEY, Q.C.:

Q. This is H & E staining, I take it?

MR. PARKS:

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A. H & E stain, yes. The checking of the block versus the tissue that's on the slide is one of the most critical things you can do, because once that slide passes that point, it is assumed that that tissue belongs to that patient, and because you're working with several blocks at a time at the microtome, picking up the wrong piece of tissue happens. We're human. It happens in every lab. And if you have another QC check where you bring everything back together and you hold the block and the slide, you can tell that the tissue is the same thing or is not the same thing, and that is one of the most crucial QC checks, because once those blocks and slides are separated, this now represents the patient and if it's not the right thing, it has grave potential. So I recommend that at that bench, the blocks come back to the slides and a visual check is performed at that point.

COFFEY, Q.C.:

Q. It goes on "there is evidence of troubleshooting with small isolated corrective actions taking place, but on overall QA, the use of the QC information being produced is

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not evident. This valuable information is being collected, but needs to be used to take corrective actions throughout the process in order to reduce the occurrence." I take it the potential for negative occurrences. "The QA processing of the QC information, the troubleshooting and the ultimate corrective action need to be assigned to a position in the lab." I'm going to ask you, Mr. Parks, to comment upon this. What was it--and I think you've alluded to this earlier today.

MR. PARKS:

A. It's the lack of connection of--there is evidence that people are noticing problems. Problem that my sections won't cut properly. If you take that information and you just document it, it's not really providing anything to the lab. QC/QA, total quality management means taking all your information and constantly looking at where the problem may be occurring and making corrections, and you can do one part and not do the other. So the system is partway in place. They are documenting. They are noticing. We now just need to see this all being tied together and

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one of the things is, again because there's so much staff flux, there's not a lot of stable staff. There's people doing jobs that they don't know the thing. If you assign it to a position, a senior position or something in the lab, where the person is responsible--and it doesn't have to be the same person all the time, it can be a position that your seniors rotate through, that person gathers this information, looks at the QC and the QA and says "okay, we got a problem here" and it's tying it together and one way of doing it, especially when you don't have a lot of experienced staff, is to have one person with more experience running this sort of procedure and training another person along with him. It can be one person's in charge of it, but another person can help them with it.

As your staff becomes more experienced and more stable and you end up with a bank of technologists with five-ten years experience, this starts to happen on a more daily basis, where someone will say "we got a problem here." But when you don't have it tied together, you're not making the adjustments

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necessary. So by assigning it to a person with some experience and giving them the responsibility and also the authority to act on what they've discovered, it would start to tie the whole thing together at this point.

COFFEY, Q.C.:

Q. I take it, as far as you could tell when you were in the labs here in St. John's, there was no one person who had that, particularly at the General?

MR. HEWLETT:

A. There was, what we call a VIP -

MR. PARKS:

A. VIP.

MR. HEWLETT:

A. - but they just didn't seem to be--it was only for one part of it.

COFFEY, Q.C.:

Q. And which part was that?

MR. HEWLETT:

A. That was sorting the embedded blocks and matching them with the prelabelled slides and the worksheets and assigning the work to the appropriate microtomist.

COFFEY, Q.C.:

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Q. Yes. But that, I take it that person or person in that role should be, as well, involved all the way out through?

MR. HEWLETT:

A. Should be doing troubleshooting.

COFFEY, Q.C.:

Q. Seeing what's happening in the baths, you know, is the tissue okay? Is anybody having a problem?

MR. HEWLETT:

A. Exactly, yeah.

COFFEY, Q.C.:

Q. And if so, going back through as to why this is happening, connecting all the dots, as it were.

MR. HEWLETT:

A. Exactly.

MR. PARKS:

A. Exactly.

MR. HEWLETT:

A. See, it's one thing to--I mean, basic laboratory practice is to record temperatures of your ovens and refrigerators. So you would have an oven that's a 37 degrees Celsius oven, and you check the thermometer and write, okay,

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today it's 37, on the little sheet and then walk away. But what happens if it was 25? Would you just write 25 on the sheet and walk away? You know, there's a reason for the change and it's the responsibility of someone to do the QA.

COFFEY, Q.C.:

Q. Having noticed -

MR. HEWLETT:

A. Not just record the data.

COFFEY, Q.C.:

Q. Having somebody to do something about the actual alteration?

MR. PARKS:

A. Exactly.

MR. HEWLETT:

A. Exactly.

COFFEY, Q.C.:

Q. If we could then, because you do make here, an observation. You've written "we have nothing but praise for the laboratory and the bench staff in adopting such an excellent and extensive QC documentation program. If the resulting QA activities are completed, documented and acted upon, the loop will be

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closed, resulting in an exemplary total quality system," which I take it is your point, Mr. Parks?

MR. PARKS:

A. Exactly.

COFFEY, Q.C.:

Q. Here, at page eight, under the heading "Staffing" you've written "the laboratory action plan, see Appendix 3," and I'll take you to that, "is an interesting document with lofty, but attainable goals. Regrettably, however, we consider the objectives to be listed in the wrong order of emphasis. We believe the last objective to be the most crucial in attaining the first three. The recruitment, training and maintaining of qualified staff has to be the primary goal of the histology division. Histology is a laboratory discipline that requires very specific skills that need time and practice to develop and hone, and only when histology is able to retain and develop staff will the lab stabilize. The mix of staff required by the histology lab will have to be developed from within. If the movement of staff in and out

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of histology continues, the right mix will never be achieved. Staff in the histology lab is in constant flux as a result of the accepted culture of laddering and staff bumping. Considerable effort and resources are being expended on bench training, only to have that person move out of the division and then require retraining upon their return months or years later. This is counterproductive to a dedicated, highly skilled and productive technologist work force. There is a noticeable disconnect between individual work areas within the laboratory and the management goals. Strong leadership in the laboratory is needed to overcome the current culture, along with a commitment from the hospital administration to create and maintain permanent positions in this laboratory area.

Two small areas in the histology laboratory, namely the gross room staffed by the PAs and the IHC lab, have had some success in acquiring and maintaining their staff. Both areas are showing improved morale and have achieved observed improvements in

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consistency and quality of work. The culture within these two areas is noticeably different. The staffs are engaged and enthusiastic about their roles and interactions within the entire pathology department.

The implementation of new technologies requires much more than purchasing new instruments. It requires a strong core group of experienced technologists with intimate knowledge and deep understanding of the current technology and willingness to learn and apply the new technology. The application of any new technology without this experience, knowledge and understanding can have dire consequences.

At the current time, there is a need to integrate the core of permanent staff in order to build a cohesive unit that can work as a team. The continued improvement of the QC/QA program through assignment of individual areas of responsibilities would be a primary goal.

The laboratory action plan should be rewritten to reflect a realization of the importance of staff in attaining the goals of

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the laboratory. One suggestion is presented below" and then under, in the next page, under laboratory program, I take it this is your suggestion, between the two of you?

MR. PARKS:

A. Yes.

COFFEY, Q.C.:

Q. It's "an action plan to provide a comprehensive, timely, high quality service utilizing human resources" and human resources is italicized here.

MR. HEWLETT:

A. That's because we changed the word.

COFFEY, Q.C.:

Q. "And available technology in an efficient manner within existing financial capacity," and then under objectives, there's numbers one, two, three and four, and I take it you've reordered the one, if we look -

MR. PARKS:

A. And rewritten the one.

COFFEY, Q.C.:

Q. And rewritten it slightly.

MR. HEWLETT:

A. Number four was that number one position.

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COFFEY, Q.C.:

Q. In Appendix 3, you've--which is the existing laboratory program action plan and objective that you were shown here in St. John's -

MR. PARKS:

A. It's posted on the wall in the laboratory.

COFFEY, Q.C.:

Q. - you've reversed--under action plan, you put human resources first, utilizing human resources, and let me get this right, utilizing human resources and put available technology second. You reversed the order in which they're stated, and you've moved what is here number four, one, two, three, four in objectives, number four objective which on the wall in there says "to ensure that there is a proper number of qualified staff, the correct skill mix of staff and to utilize human resources in an efficient manner." You've utilized that, if we look back to page-- changed the order, moved that into number one as an objective, and changed the wording slightly to the following, your wording is "to create an environment that attracts and maintains the proper number of highly

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qualified staff, the correct skill mix of staff and encourages their ongoing professional growth." That's your, I take it, your considered judgment?

MR. HEWLETT:

A. Absolutely.

MR. PARKS:

A. Yes.

COFFEY, Q.C.:

Q. Number two, and I believe numbers two and three, in effect, are the same, although number three, you're made a change. Number two, you've written "to provide the Health Care Corporation of St. John's and/or the Province" and that would be really in effect "Eastern Health and/or the Province with comprehensive lab services and also expand the test menu to provide in-province testing." Now, gentlemen, here, the HCCSJ, I'm just going to--here, this is what you found written on the wall?

MR. PARKS:

A. This is what we found, yes.

MR. HEWLETT:

A. This is what we found written on the wall.

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MR. PARKS:

A. And we did not change two and three, or number one. We just reordered them. That is what is -

COFFEY, Q.C.:

Q. HCCSJ is what's there on the wall?

MR. PARKS:

A. Yes.

COFFEY, Q.C.:

Q. Okay, and two is the same, I gather, in comparing them.

MR. PARKS:

A. Yes.

COFFEY, Q.C.:

Q. And number three, they had written "to make available the most up-to-date laboratory technology, ensuring the HCCSS lab program is a leader in Canada" and I'm going to look back at your suggestion, which is you've suggested, number three, "to make available the most," and you've added the word and italicized it "appropriate, up-to-date laboratory technology, ensuring the HCCSS lab program is a leader in Canada." Why did you add the word "appropriate"?

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MR. PARKS:
A. Well, just applying technology, the most up-to-date technology, is not necessarily going to give you better results. Technology is being developed by people who are not always in the field, and they don't understand everything that they're doing, and for example, there's some of the equipment out there that speeds things up and makes things faster, does not necessarily fit into what you're trying to do with your laboratory. So up to date, I mean, that's really not what you're aiming for. You're looking for the most appropriate for what you are doing in your lab and what services you're providing.
COFFEY, Q.C.:
Q. Mr. Parks, as an example, are you familiar with the Sakura Express?
MR. PARKS:
A. I've never used one, but I do--I have done quite a bit of reading on it.
COFFEY, Q.C.:
Q. And the idea of speeding up, I take it that's one of the selling points, as it were, with that? It makes tissue processing faster?

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MR. PARKS:
A. The Express is sold as the machine that helps you lean your lab by using small batch technology and rapid turnaround time. You know, you have it turned out in an hour and 20 minutes or whatever it is, and that's a whole new technology. It uses solutions that are not what we use on our current processes. We are not privy to what actually is in the solutions. They're proprietary reagents. So you are trying to do something now that you want standardized for your fixative or for--you want to standardize your fixation or you want to standardize any process, this here is using stuff that we don't even know exactly what is going on. So you're left with tissue that may not be compliant with any other of your stuff required down the way.
COFFEY, Q.C.:
Q. And I take it you don't have one in your lab?
MR. PARKS:
A. No, I do not.
COFFEY, Q.C.:
Q. Under summary, at page ten, you've written "during our four-day visit to the Health Science Centre and St. Clare's Mercy sites, we observed a significant amount of quality control, QC and documentation being performed in all areas of the histology laboratory. We also observed pockets of corrective actions being taken and documented based on the results of the QC, but there is some disconnection of the information and it's use in total quality improvement of the over product of the laboratory. There has been a real effort in areas of the lab to determine what are the current patterns of practice and implementation of these practices. Fixation time and tissue sample thickness is one of the most obvious applications of this," which I take it, from your perspective, was a positive?

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MR. HEWLETT:
A. Right.
COFFEY, Q.C.:
Q. And then you've continued, "the disconnect of the information and the need for corrective action is most likely due to the instability and movement of staff in and out of the histology laboratory. Staff are being trained on specific benches to get the most productivity out of their efforts, without knowledge of the whole process. This has been happening for years and has resulted in an inability to use all the information being collected. A bright note in regards to this is the training taking place at this time of two new full-time permanent employees. They have started their training at the front of the histology process, grossing, and have been progressing through the lab just as a specimen would. We firmly believe that if the staffing can be--if the staffing can be stabilized and the right people are recruited and retained in permanent positions, the lab will be able to develop a whole picture approach to total quality management."

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And finally, compliance, you've written "we believe the laboratory efforts to date in regard to the handling of fresh breast and other specimens," that would be fresh breast specimens and fresh other specimens, "fixation policies, procedures and grossing practices places them well in compliance with and even exceeds the important pre-analytic sections of

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the Canadian consensus guidelines for HER2/neu testing, the ASCO CAP guidelines for HER2 testing and the soon to be published ad hoc committee ER testing guidelines. With further modifications to the tissue processing and embedding protocols, correcting any potential remaining processing insufficiencies, the effects of poor tissue preparation in IHC testing will be a thing of the past."

I take it, gentlemen, that remains your-- they remain your views, in terms of the two labs here in St. John's?

MR. PARKS:

A. Yes.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. Mr. Hewlett, perhaps before I go on to the labs outside St. John's, I'll ask you, gentlemen, in relation to the training of technologists, histotechnologists in particular and immunohistotechnologists in more particularly, from your perspective--I'll ask you first, Mr. Parks, what do you believe is perhaps the most desirable approach to

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that?

MR. PARKS:

A. Well, you have to start off with the base knowledge of it, which it's nice when you start to move people into these newer, especially immunohistochemistry and stuff, that they have taken some background courses, either through online or correspondence courses, such things, so they get the background. I find some of the best training is always in house, even if you have to bring somebody in from outside to do it. It's much better to train in the environment you're going to be working in, as opposed to taking someone off to, you know, another institution. If you have someone there then, you're seeing exactly what you're working with, because that is what you want to standardize your process on, is what you are going to work with for the rest of your career in that area. So I believe strongly in a lot of in-house training, but some educated background, usually through correspondence courses and such things. But once they're there, there is very extensive and continuous interaction with

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other people in that area, plus with the pathologists. It's critical.

COFFEY, Q.C.:

Q. Mr. Hewlett?

MR. HEWLETT:

A. I would go back a little further. There is a perception out there that because somebody is a certified technologist that that means they can do anything in the laboratory. I think it's crucial to remember that certification as a technologist is at the entry level. In other words, they have the basic knowledge and skills to perform a wide variety of tasks within a medical laboratory situation, but that's just the beginning. It's for the safety of the public that they're certified and registered in some provinces. That's just the beginning. It would be unrealistic to expect a newly certified technologist to walk into-- and this is in all disciplines within the clinical laboratory--to walk into any particular institution and be immediately up to speed on the latest molecular techniques. It's not going to happen. It's not part of their basic training, nor should it be. So

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that means there has to be some form of in-house training and development, and histology is a lot like that. As you heard it mentioned - seen it mentioned in the report, since skills can only be acquired by time and practice, microtomy is a classic example, the more you do, usually the better you get, and that's not part of the basic training. Yes, they learn how to physically do it, but then it's a question of time and effort and I think there has to be that recognition and each new thing that comes into the laboratory, and there are a stunning array of them at this particular point in history, immunohistochemistry being a class example, that also requires additional knowledge and time and experience on top of what you already have. It's a lifelong learning process, and that needs to be addressed in the lab, and I agree with Bill that one of the best places to obtain that experience is where you're going to do it. That, of course, has some staffing implications. You need to have somebody on staff who can take over that training of the new people coming along, and so that has to be

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into the budgetary process to allow that kind of development to occur. This is where, if you look at things like productivity, yes, that's an important goal, but there's the productivity of the upcoming technologist is crucial.

COFFEY, Q.C.:

Q. Yes.

MR. HEWLETT:

A. And if all you're focused on is how many H & E's you can bang out in a day, I'm sorry, sooner or later that system is going to fail.

COFFEY, Q.C.:

Q. If you're not paying attention to the quality of what you're doing?

MR. HEWLETT:

A. Absolutely.

THE COMMISSIONER:

Q. The current process for educating - giving the technologists that basic level, would that, for example, contain any kind of basic introduction to IHC which could be built up or is IHC not even discussed in their world?

MR. HEWLETT:

A. At the basic level, it's applied not

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specifically to IHC, but antigen antibody interactions are part of blood banking and a number of other disciplines, so at that level, yes, absolutely, it's one of the competencies required.

THE COMMISSIONER:

Q. Okay. So you would come out of your basic training with knowledge that would enable you to, can I say, relate to what you then get by way of instruction within the lab about IHC?

MR. HEWLETT:

A. Absolutely.

THE COMMISSIONER:

Q. Okay, and you said that you thought - you added not only that they sort of not have that advanced training in sort of the academic setting, but you believe that that was appropriate. You need that additional feature of working in a lab to really understand -

MR. HEWLETT:

A. Absolutely.

THE COMMISSIONER:

Q. How to do it, or is that what it is - you need to have the experience to know the kinds of things that you two gentlemen know about why

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this slide doesn't look right, even though it might look like the thing in the picture in the textbook?

MR. HEWLETT:

A. And the same is true, for instance, for pathologists. I mean, they learn the basics in medical school and residency and in training, but once they start on the job and see the day to day cases coming through, it's a constant learning experience, and the more experience they acquire, the better they get at it.

THE COMMISSIONER:

Q. Mr. Parks, in your laboratory, is there a person with the job of keeping the education up to date, or is that considered to be the job of every old hand, or how do you organize transferring the information?

MR. PARKS:

A. Well, since I've taken over - I do a lot of the training myself. I'm in charge. I'm in my lab almost all day. I tend to do my paperwork after everybody is gone home. I have a senior tech who works with me, and we do the training together. We're on the same

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page. We discuss how we're training people, and we have a - and I'm training people all the time, a very structured way of training. When you come in, you start off and work your way through and the training is continuous. Whenever there is new techniques or something, people are trained in it. We have documentation about training and the staff actually has the power that if they don't feel competent enough to perform what I've asked them to, and they won't sign the paper, I won't make them do it. So there is paperwork that says, yes, I have been taught this, I've signed that I taught it or my seniors taught them, and then they sign that they feel competent enough to perform that task, and we monitor. In Ontario, we have a competency assessment on a yearly basis where I go through and I will - even my 26 years of service techs, I assess their competency of doing each task on a yearly basis, and we sign off, and if there's - if someone even tells me I haven't done this task in eight months, I need to be retrained, we will go through retraining and work with them on the bench.

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It's time consuming.
THE COMMISSIONER:
Q. Yes.
MR. PARKS:
A. And very costly. I mean, it takes two people out of the lab on a lot of basis, but, yes, that's how we do it.
THE COMMISSIONER:
Q. And I'm interested in your sort of continuation by virtue - by reason of the fact that you are each year signing off on someone's competency, then you also have to determine whether or not they're continuing to practice in that area and their knowledge isn't stale?
MR. PARKS:
A. Exactly, and because we're all in the histology lab, I try - I do the staffing and I try to rotate everyone of - not through immuno, I have to say that. Immunohistochemistry is run very independent of the main histology, and only eight people are trained to do immunohistochemistry, and those ones when they go in there get extensive training in that area.

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THE COMMISSIONER:
Q. Uh-hm.
MR. PARKS:
A. But the people in the main lab, which is my domain, and because of the size of the lab, we've split into two entities - we still operate together and we share staff, but there's very extensive training in the specialized one as well done by the charge tech of that area.
THE COMMISSIONER:
Q. Do you know how long it would take for somebody who is entering into the IHC section of the lab to get that little sign off certification to be able to do various procedures?
MR. PARKS:
A. It is a fairly large amount of pages, and I can tell we have people who have been there training for six or eight months and haven't covered all aspects of it. So they only cover certain areas of the lab - it's fairly extensive.
THE COMMISSIONER:
Q. And when they went into IHC, would they likely

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to have already been skilled in -
MR. PARKS:
A. They would have been skilled in histology.
THE COMMISSIONER:
Q. Histology.
MR. PARKS:
A. Definitely, because the only people that can go into IHC are from the histology lab.
THE COMMISSIONER:
Q. That's your route in.
MR. PARKS:
A. That's your route in.
THE COMMISSIONER:
Q. First you have to, as a rule, master histology?
MR. PARKS:
A. Yeah, and then you get to rotate out again every several months to keep your other skills alive.
THE COMMISSIONER:
Q. Okay.
MR. PARKS:
A. They come back out to me. We have trained eight, but there's only five positions, so they rotate into there on a - by month by

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month basis, and there's even an interview and a written exam before they go in there, and they're actually scored and if they don't score on a certain level, they wouldn't be considered for the position in there, and it's - the exam to go into IHC covers the basics and a little bit of advanced. So they've had to study or at least taken courses to get to that point.
MR. HEWLETT:
Q. I was just going to add that one of the reasons it's difficult to say is it depends on the elaborateness of the immuno department. If they're running half a dozen markers, then that's relatively easy and would take a few months. If, like my lab, you're running close to 300 markers, that takes a lot longer because the technologists have to become familiar with all of those expected reactions and cross reactions. So that could take a considerable length of time. You know, a year at least, at the very least, I would think, depending on how often one is exposed to a particular marker.
THE COMMISSIONER:

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Q. Okay, and would - you both seem to have had exposure to lots of other laboratories. Would you believe that that kind of time frame would be the accepted view of what the appropriate time frame would be in the rest of Ontario, for example?

MR. HEWLETT:

A. I would think so, yeah.

MR. PARKS:

A. It depends on - I'd have to say it depends on the laboratory, say, and the availability of staff. I know in some places they're put into places - into that with less training because they can only be trained by the person who has as much training as they have in that place.

THE COMMISSIONER:

Q. It seems to me that that's the - that creates a problem because unless you had sort of vagabond teachers running around the country, you really have to have people within your organization who have not only the knowledge, but the capability of imparting that knowledge to people who are coming through the door in order to create your successful program and maintain it?

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MR. PARKS:

A. And that is one of the things about culturing your staff and finding people in your mix that have that ability and to use it, and help them develop the ability, and that's what I've had to do because one person cannot do all the training, and that's why we have several people doing training, but you look for that in the staff within and bring it along and help them. Again there's lots of external education through the Michener Institute, the CSOT. There's courses out there online or in correspondence that you can use to bring your knowledge up and then apply your knowledge in the workplace. There's ways to do it, but I know a lot of places will bring in, as you referred to, the vagabond teacher. Two of us are kind of different -

MR. HEWLETT:

A. Welcome to the vagabonds.

MR. PARKS:

A. Yes, we do get asked - I get asked quite often to come in and address a specific area of a lab and bring my expertise, and impart my expertise on the people in the thing, and then

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maintain an internet connection with them so that they can continue to contact me with issues and problems.

THE COMMISSIONER:

Q. That seems to me to be the short - potential shortcoming of having someone come in from outside. You would come with a lot of knowledge and, you know, but let's face it, we all only retain a portion of what you tell us in any one day.

MR. PARKS:

A. Exactly.

THE COMMISSIONER:

Q. And thank God for transcripts, in my case, but in order to put that into practice and the questions that are not going to come up until you walk through the door, are not going to be answered unless you continue to be available to these people.

MR. PARKS:

A. Exactly, and that's one of the things that I can tell you since the late 90s and stuff with the internet, it's been a - it's great because people are firing questions as they happen in their lab and we can answer them that night

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sort of thing. It's part of the connection, and a lot of people are sending slides for evaluation, and, you know, they send stuff in and ask what do you think of this, so you - you offer your opinion and you try to help them with what you can do, but it is difficult because not every technologist wants to be a teacher, not every technologist wants to spend time studying.

COFFEY, Q.C.:

Q. Mr. Parks, if I could, since you're talking about movement of people in and out of the IHC part of your own lab -

MR. PARKS:

A. Uh-hm.

COFFEY, Q.C.:

Q. In Ottawa, from histology into IHC, and they're trained there, but even the IHC technologists, I take it, who are fully qualified and accepted to do all the procedures there, there's a system in place to occasionally rotate them back out into histology because, as you put it, to keep up their skills and exposure to general histology?

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MR. PARKS:
A. Exactly.
COFFEY, Q.C.:
Q. Within histology itself, leaving aside the IHC end of it, I want to ask you to comment to the Commissioner about what you observed at the General Hospital in terms of people being at, like, a particular bench for extended periods of time, if not a single day, even for weeks at a time or months at a time, based upon your conversations with them, compared to your own approach in Ottawa in terms of moving people through the lab, and I'm talking about people who are already trained now -
MR. PARKS:
A. Okay.
COFFEY, Q.C.:
Q. Not people who are in the training process.
MR. PARKS:
A. With my staff, I rotate them - we have - I've actually changed quite a bit the way the work flows, but I have my staff who comes in and actually works - they don't sit at one spot all day. They'll come in and they'll embed for one hour. Every staff in my department

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can embed tissue. They all come in on different shifts and they embed one of the processors that finishes. They then get up and proceed to cutting, which is the next step, and they'll cut for so many hours, and then they'll go and they'll do slide sorting or solution making, so there's a constant flow of work, plus - that's the daily event, but also on a weekly event, you change from what your responsibilities are for the day. So one week you'll be doing frozen sections and embedding and cutting, and then the next week you'll be doing - you'll be responsible for decals. So we mix up constantly so everybody in the lab can fill any position in the lab, and the more that you're interacting with each aspect of the lab, the more you're able to become part of the QC/QA - you're part of the puzzle and you put it together. So there's a lot of things with that, always being involved in many aspects of it as opposed to just doing one thing. You don't see the big picture, and that to me is critical that staff sees the whole picture of what they're doing, and you understand the consequences of what you do

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here when you go and handle it over here, and it actually improves all your technique all the way back through because you - this didn't do well because I didn't do this well. If you never do this thing, and you're only doing this, you're not getting the interconnect. So we do that on a daily basis, you move through things, and on a weekly basis, you go through different rotations, and everybody in my lab, I still - I have to say I have quite a few people in training because I have a lot of staff, but once they're fully trained in the histology area, they can handle any bench, and they will be expected to handle any bench, special stains, H & E, everything. So everybody knows everything that's going on.
COFFEY, Q.C.:
Q. Is there any - leaving aside the lack of exposure to other parts of histology if you're just on the one bench, and you've spoken about that, is there any actual practical downside to being - doing a particular thing for six to eight hour a day? Can you tell the Commissioner about that?
MR. PARKS:

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A. Ergonomics has become a major issue in histology because your actions are extremely repetitive, especially on the microtomy and that, you're doing very short actions, but you're repeating them hundreds and hundreds of times, and if you sit and embed for twelve hours a day or the eight hour shift, you are going to be doing the same repetitive motion so many times that you're going to cause a joint problem. Before I became in charge of the lab, we have lost several good technologists due to repetitive motion syndrome, shoulders, elbows, wrists. One of the girls had to have her whole joint of her thumb replaced because of this, and the common - in the old days, it used to be, well, if you do something continuously, you get better at it and more efficient. Studies show that is not true. Actually, you reach your peak of efficiency and after an hour and a half of doing something repetitively, your efficiency falls off, plus you're injuring your body. So by looking at that and seeing exactly where the most repetitive was happening, I adjusted the lab. With my manager, we looked at

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things, and we adjusted. So you work through the lab so you don't do the same repetitive motion all day, every day, and ergonomics now, because there's very few technologist out there to hire, we can't afford to lose them. So you have to provide an environment that allows them to be healthy all the way through.

COFFEY, Q.C.:

Q. Exhibit P-3366. This is a document entitled, "A process review of the Western Memorial Regional Hospital, Pathology Laboratory, under the Western Regional Integrated Health Authority, October 2nd, 2008". It's a report by Bryan Hewlett. This is your report, Mr. Hewlett?

MR. HEWLETT:

A. It is.

COFFEY, Q.C.:

Q. And if I could ask you to bring up, please, Exhibit P-3367. This is a document entitled "A process review of the James Paton Memorial Regional Health Pathology Laboratory under the Central Regional Integrated Health Authority on October 3rd, 2008", by Bryan Hewlett. This is a report for the Gander Hospital, Mr.

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Hewlett?

MR. HEWLETT:

A. Yes, it is.

COFFEY, Q.C.:

Q. And Exhibit, please, Registrar, P-3368. This is entitled "A process review of the Charles S. Curtis Memorial Hospital Pathology Laboratory under the Labrador Grenfell Regional Integrated Health Authority" on October 6th and 7th, 2008, by Bryan Hewlett. This is a report involving St. Anthony's Hospital?

MR. HEWLETT:

Q. Correct.

COFFEY, Q.C.:

Q. Mr. Hewlett, I appreciate that you spent less time, of course, at these institutions than you were able to at the hospitals here in St. John's.

MR. HEWLETT:

A. Right.

COFFEY, Q.C.:

Q. And that's - amongst other reasons, because of the logistics, but in the main in terms of your visits to the hospitals in Corner Brook,

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Gander, and St. Anthony, what were you looking for just generally, what was your approach?

MR. HEWLETT:

A. Again basically the front end, how samples were being obtained and fixed and processed up to the embedding section and cutting stage.

COFFEY, Q.C.:

Q. And the preparation of a block, whether it ends up in Mount Sinai having ER/PR done on it or in St. John's, or wherever it ends up, for breast cancer, for example, tissue, you would see the front end process?

MR. HEWLETT:

A. Exactly.

COFFEY, Q.C.:

Q. You examined it, and this would apply not only to breast cancer tissue, but presumably to all other pathology tissues that were going into blocks?

MR. HEWLETT:

A. I looked at what was available during my time there to look at.

COFFEY, Q.C.:

Q. If we could look, please, at 3366. This is the one involving Corner Brook. Perhaps you

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could just tell the Commissioner an overview of what you did in Corner Brook?

MR. HEWLETT:

A. It was a truncated version of what we did in St. John's using a similar checklist and so on, and looking at essentially the same parameters. First and foremost, was the front end, is there appropriate specimen receipt and handling, fixation, and processing. Essentially that was the main portion of it, but I also looked at the policy and procedure manual and had some discussion with both pathologists who were there at the time, and the technologist involved. I also had a look at some of their quality control assurance records.

COFFEY, Q.C.:

Q. And having made your observations and interacted with the staff there, you prepared this report?

MR. HEWLETT:

A. Uh-hm.

COFFEY, Q.C.:

Q. Okay. I want to take you through some of the report, if I could. Here under - you have an

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introduction that sets out the date, October 2nd, 2008, and in essence, if you review the first three paragraphs, it's very similar to the introduction to the St. John's report?

MR. HEWLETT:

A. They all are. I followed the same format.

COFFEY, Q.C.:

Q. Same format, and here you did note that you found the pathologists and the technical staff to be very forthcoming and honest in their answers and dedicated to the tasks they were performing. I take it that was true throughout the province?

MR. HEWLETT:

A. It was. It was really remarkable and the interest they showed in what was happening, and the desire they felt to, as it were, get things right at the front end, and also to interact, I think, with someone from, as it were, outside their immediate area. The one thing that did strike me throughout all of this was the real lack of continuous professional improvement availability. These people are hungry for more information, all of them, pathologists and technical staff.

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COFFEY, Q.C.:

Q. Here under fixation, you've noted in relation to Corner Brook, "Observation of the specimen receiving area, specimen triage, and the grossing of the specimens, along with review of documentation, leads me to believe that the tissue of fixation has been largely addressed in principle. Specimens from the OR are delivered by a runner on a regular daily schedule. Deliveries are at 8:30 a.m, 11:30 a.m, and hourly thereafter until 3:30 p.m. Breast samples are delivered immediately on procurement and lab staff is notified".

Mr. Hewlett, if it turned out that there was surgery for non-breast samples, pathology, after 3:30, from your perspective, should it remain in formalin if it was being (unintelligible).

MR. HEWLETT:

A. This is where it got very difficult. There seems to be a misconception out there about refrigeration.

COFFEY, Q.C.:

Q. Okay, and we're -

MR. HEWLETT:

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A. May I elaborate?

COFFEY, Q.C.:

Q. Yes, if you could. What I would like to do is I'll read through this and then have you elaborate on it because this kind of sets the background for it. It says, "Requisitions are date and time stamped as to procurement and time received by the lab. Specimens procured after hours are placed in fixative and stored in the refrigerator until the next day. This is sub=optimal since fixation is greatly delayed at 4 degrees celsius. This practice seems to stem from a misunderstanding of the role of refrigeration in handling tissue specimens. Only fresh tissue should be refrigerated if the pathologist/oncologist is delayed for an hour or so. Cooling tissue slows down the degeneration process slightly and provides a limited additional time interval before the specimen must be fixed. If the specimens are small, one centimetre in largest dimension, they are best placed in formalin and fixed at room temperature. If the specimens are larger, then the pathologist/oncologist should be notified to

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deal with them". Go ahead.

MR. HEWLETT:

A. To actually put specimens, as was happening, put specimens into formaldehyde and then refrigerate them is really counterproductive. The difference in - very little difference in penetration rate, although it is slower, the real difference is in the fixation rate. The chemical reaction is dramatically slowed at 4 degrees centigrade, dramatically.

COFFEY, Q.C.:

Q. In the mean -

MR. HEWLETT:

A. In the meantime, the centre of the tissue is rotting away, so to speak. I do understand to a certain extent how such confusion can arise because there is a misconception out there, particularly in the research community, that fixation is best done at 4 degrees celsius to minimize these autolytic and other changes that occur on cell death, and that's a common myth. If you read any research article, they'll say, you know, material was fixed at 4 degrees celsius. This is not a good idea at all. It's one thing to use a refrigerator,

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and I believe Trish Wegrynowski mentioned this in St. John's, to have it available as a stop gap until somebody can get to the tissue, when you slow down these changes, it gives a greater time interval prior to fixation and that's a good thing, it's certainly not intended to fix in the refrigerator because essentially you won't.

COFFEY, Q.C.:

Q. So you made this observation in Corner Brook, and then it goes on, "The fixation time of most specimens is now 24 hours or longer with the exception of a few rush specimens".

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. "The pathologists are preparing larger specimens in such a manner as to optimize fixation prior to grossing".

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. So you're satisfied as to that. I did want to ask you about this delivery of breast delivered immediately on procurement and lab

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staff is notified, and bearing in mind, hourly until deliveries occur.

MR. HEWLETT:

A. This is all other specimens.

COFFEY, Q.C.:

Q. Others?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And from your perspective, though, if, for example, a specimen only became available in the OR after 3:30 and didn't make the last run, as it were?

MR. HEWLETT:

A. The lab staff actually do a final check.

COFFEY, Q.C.:

Q. That was the -

MR. HEWLETT:

A. On the refrigerator.

COFFEY, Q.C.:

Q. But it was as well, I take it, not only for breast - your understanding it was not only breast samples, they were checking for everything?

MR. HEWLETT:

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A. All samples.

COFFEY, Q.C.:

Q. Everything to make sure they were all downstairs by the time they go home for the day?

MR. HEWLETT:

A. As much as possible, yes.

COFFEY, Q.C.:

Q. And then it goes on, "Procurement time, date, and time received in the lab, and time in fixative for breast specimens and time for grossing are all recorded", and you note that, "This information provides documentation that's available to users of the tissue block for all future studies", and having made some more comments, you say, "this is in compliance with the existing Canadian Consensus Guidelines for HER2/neu testing and the soon to be published guidelines by the Ad Hoc Committee on ER Testing". Then, Mr. Hewlett, we have the same text in italics as was in the report involving St. Clare's and the General about the 10 percent buffered formalin.

MR. HEWLETT:

A. Because it was the same product.

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COFFEY, Q.C.:

Q. And that applies, I gather, throughout the province?

MR. HEWLETT:

A. It applies across all the locations. Some people are checking the pH of their product directly. Some institutions are using a dip stick which is wildly inaccurate, but at least they're doing something, and I recommended that appropriate pH meter should be available.

COFFEY, Q.C.:

Q. You've also noted here in relation to Corner Brook under this section, "All grossing is performed by the pathologist there". They don't have PAs.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. "Using CAP", which would be College of American Pathologists.

MR. HEWLETT:

A. American Pathologists, yeah.

COFFEY, Q.C.:

Q. "Checklist for various specimen types for inclusion in a synoptic reporting format.

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Special instructions for the technologists are provided on process work sheets as necessary. The technologists report only occasional problems with tissue thickness. These occasional problems are brought to the pathologist attention".

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. You were advised of that?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And then under "Processing" you've noted the following, "There is some evidence that an occasional intermittent problem exists with the processing of the tissue blocks. A random review of the large blocks in the storage files found only occasional blocks that showed evidence of inadequate processing. The tissue in these blocks was retracted from the surface and dry. This is indicative of tissue that was insufficiently cleared and/or infiltrated with paraffin. I did not find blocks containing smaller pieces of tissue that

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showed similar inadequate processing. This indicates that sporadically large tissue blocks were likely too think to be adequately processed by the routine processing schedule. It should be borne in mind that such occasional events occur in most histology laboratories due to momentary lapses in judgment of tissue block thickness during grossing. Observation of the pathologist during grossing of large specimens showed the appropriate selection of tissue thickness being placed in cassettes." And that was what you actually watched while you were there?

MR. HEWLETT:

A. Yes, yes.

COFFEY, Q.C.:

Q. In terms of what was currently going on that day.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. "Another artifact observed, rarely in a few blocks was a very evident interface line separating the tissue and surrounding supporting paraffin. This can occur if the

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tissue is allowed to cool or is drained of molten paraffin before being placed in the mold during the embedding process." Which I take it is similar to the -

MR. HEWLETT:

A. Cut and paste.

COFFEY, Q.C.:

Q. - situation in St. John's. You continue, "A review of the schedule used on a processor showed that there is an inadequate number of graded alcohols in the dehydration sequence. The sequence is 50 percent, 70 percent, followed by a jump to 100 percent. It is recommended the sequence be changed to 70 percent, 80 percent and 95 percent, replacing the first of four 100 percent alcohols. This would match the recommended sequence for the St. John's laboratory."

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And did that apply elsewhere?

MR. HEWLETT:

A. Yes, it did. There seemed to be a theme that whoever set up the processing equipment, to

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also sort of set up the program.

COFFEY, Q.C.:

Q. And it goes on, "It was noted that a xylene substitute, citrisolve, was being used for the clearing process. Although in itself, use of such substitutes may be a more ecologically friendly approach and is to be applauded, such a change in process reagents may have an impact on subsequent IHC. The soon to be published Ad Hoc committee recommendations on ER testing state use of such substitutes needs to be cross validated against material using a hundred cases processed in a conventional way. The reference lab performing IHC needs to be informed of this and close co-operation would determine suitability of this process change." Could you tell the Commissioner and elaborate a little bit on that?

MR. HEWLETT:

A. We don't understand the effects of some of these reagents on the immunohistochemistry, it's simply not been studied.

COFFEY, Q.C.:

Q. And Citrisolve is one of those, I take it?

MR. HEWLETT:

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A. Any xylene or toluene substitute, they are the unconventional clearing agents which are used. There are lots of them out there. But there is no study that I am aware of or that the Ad Hoc committee is aware of that indicates the effect of these things. There may not be an effect, but the problem is that we don't know and so a traditional way of finding out is to experiment and basically that's what the committee is recommending, if you're going to do this, then you should take parallel pieces of tissue from a case, put one in a conventional processor using conventional reagents, the other one in a processor using the substitute reagent, run them both and do immunohistochemistry on them and compare them. That's like a validation that you cross validate.

COFFEY, Q.C.:

Q. Now the next paragraph, Mr. Hewlett, you refer to "Observed the racks loaded in the processors had the organized cassettes packed tightly together." And I'm not going to continue to read though this -

MR. HEWLETT:

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A. Same thing.

COFFEY, Q.C.:

Q. Same thing as St. John's and the same recommendation.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. To address it. And you noted "Documentation of the processor's scheduled maintenance and reagent changes was available and indicated that this had occurred within the specified time limits." And you go on, "The two embedding centres in use were of different manufacturer, one having an empty heated holding well for the specimens, the other having a heated holding well containing liquid paraffin. Both were set up according to the manufacturer's instructions. I recommend that the embedding centre with the liquid paraffin will be used to hold all specimens during embedding with both instruments. This will prevent the blocks cooling and liquid paraffin draining from the tissues in the instrument with a dry-heated holding well. Maintenance of a liquid paraffin phase at the outside

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tissue surface during embedding will also prevent separation interfaces forming between tissue and the supporting paraffin", which is the same issue in St. John's you had noticed?

MR. HEWLETT:

A. Yeah, except we had one machine -

COFFEY, Q.C.:

Q. Doing what you were going to suggest.

MR. HEWLETT:

A. The manufacture's recommendation is to fill it with liquid paraffin, so they're the ones who said no.

COFFEY, Q.C.:

Q. "And at the microtomy work stations, it was noted that following section pick up on slides, the amount of cut sections were dry prior to staining and a hot air oven at 100 degree celsius. This includes sections that are cut to be sent for IHC. This is of concern for IHC since antigen degradation occurs more rapidly during transport of sections following high temperature exposure. The reference IHC lab should be informed of this practice"--I take it that's the lab who is doing the IHC testing.

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MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. Or producing IHC slides. "Their recommendations regarding section handling should be followed. It would be preferable to send the air dry IHC sections and allow the reference lab to dry them just prior to staining. Even more preferable would be to ship the blocks to the IHC lab for cutting."

MR. HEWLETT:

A. Correct.

COFFEY, Q.C.:

Q. And -

MR. HEWLETT:

A. And that is a considerable concern, that's much higher temperature than -

COFFEY, Q.C.:

Q. One hundred celsius, yes.

MR. HEWLETT:

A. Normally we dry slides for H&E at no more than 60 celsius. It is an important step that they be--we refer to it as baking on, that that occur. The problem is that you're shipping some distance, following that step,

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degradation of antigens is much more rapid and the unstained slide, by the time it arrives at the IHC lab, may give you a false negative.

COFFEY, Q.C.:

Q. Because it's been heated so hot, it's in the process of baking on.

MR. HEWLETT:

A. Because it's been heated--this is of concern to us in QMPLS, EQA and -

COFFEY, Q.C.:

Q. So this concern exists elsewhere too, I take it?

MR. HEWLETT:

A. Oh yes, yeah.

COFFEY, Q.C.:

Q. Extends into Ontario in certain situations.

MR. HEWLETT:

A. It certainly does, yes.

COFFEY, Q.C.:

Q. Here then, "Manuals and documentation" you refer to "The histology laboratory policy and procedure manual was briefly reviewed, although not in CLSI format, the manual covered most basic technical procedures. A complete rewrite of this manual to current

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accreditation standards would take considerable time, effort and require substantial additional resources. In addition, an overall laboratory quality system would need to be in place. This would be required if accreditation were to be pursued.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. So I take it their manual would have to be brought up to date and -

MR. HEWLETT:

A. An entire quality system for the laboratory as a whole would have to be instituted as part of accreditation.

COFFEY, Q.C.:

Q. You noted, "There is evidence of use of this manual"--that is the existing one that they had there.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. "The staff is aware of the manual and have also demonstrated their knowledge through application of several situations during my

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visit to the site. There is evidence of some QC documentation throughout the work processes and more complete documentation would be valuable, for example in microtomy work sheet with corrective actions taken. The technologists check the control slides for H&E but no record of corrective action documentation is kept. Special stain controls are checked and documented in Meditech. One of the most important QC checks in histology occurs at the H&E staining bench. Slides and blocks should be brought together for comparison after staining to ensure that a complete section of the correct tissue is on the slide. This QC check is neither being performed or documented at this time." And that's the thing Mr. Parks spoke about

MR. HEWLETT:

A. Same, exactly the same.

COFFEY, Q.C.:

Q. St. John's. "And there needs to be sign-off sheets at many of the work stations assigning ownership and responsibility for the task. Where possible, the specific case number should be listed, corrective action record

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sheets should also be in use at the same work stations. There is evidence of troubleshooting with small isolated corrective actions taking place, but an overall QA use of the available QC information is not evident. Valuable information needs to be collected and used to take corrective actions throughout the process in order to reduce the occurrence." This is the same situation as in St. John's?

MR. HEWLETT:

A. Same, exactly the same situation.

COFFEY, Q.C.:

Q. The gathering -

MR. HEWLETT:

A. By gathering some QC documentation, not nearly as thorough or complete as St. John's.

COFFEY, Q.C.:

Q. St. John's, but even of the ones they are gathering, still have to be integrated -

MR. HEWLETT:

A. Still have to be integrated and -

COFFEY, Q.C.:

Q. And under "Staffing" there's, I take it a similar comment as the one in St. John's, about -

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MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. - about the type of laboratory discipline it is and you've noted here, "The current staffing levels appear to be just adequate for the workload"--in Corner Brook this would be. "It is encouraging that a relatively new staff member is undergoing training at this time. Continuing professional development for the pathologists and technologists needs to have more resources allocated and participation encouraged. It is also not too early to be developing a succession plan." I take it because of the -
MR. HEWLETT:
A. Well I had some discussion with the people there and I said where do you get staff? Well, it can be difficult.
COFFEY, Q.C.:
Q. And here then, under "Summary: There's been a real effort in areas of the lab to determine the best patterns of practice and implementation of these practices, fixation time and the related tissue sample thickness

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is one of the most obvious applications of this. Pathologists and technologists all expressed enthusiasm and genuine eagerness to learn about the rationale behind the latest practices and techniques of tissue handling that are so necessary to accommodate ancillary testing methodologies such as IHC." And you would have understood IHC, of course, is not being done in Corner Brook itself.
MR. HEWLETT:
A. I realize that, but as we mentioned, this is the front end, they're sending stuff away, it applies.
COFFEY, Q.C.:
Q. And finally under "Compliance: I believe that the laboratory's efforts to date in regard to the handling of fresh breast and other specimens, fixation policies, procedures and grossing practices, places them in compliance with the important pre-analytic portions of the Canadian Consensus Guidelines for HER2/neu testing. ASCO/CAP guidelines for HER2 testing and soon to be published Ad Hoc committee ER testing guidelines. With further modifications to the tissue processing and

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embedding protocols correcting any potential remaining processing insufficiencies, validation of the use of xylene substitute and consultation with IHC lab regarding section preparation, the effects of poor tissue preparation on IHC testing will be minimized." I take it then, as you've noted, there's a table here which is similar to -
MR. HEWLETT:
A. It's the same actually, as an example -
COFFEY, Q.C.:
Q. Of what you were suggesting in St. John's, yourself and Mr. Parks for the tissue processor.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. In terms of the graded alcohols.
MR. HEWLETT:
A. Yes, the other advantage to this is because they're using similar machines around the province, if everybody goes on to a similar schedule and similar reagents, then effectively you standardize that part of it as much as it can be and that's a good thing.

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MR. PARKS:
A. Very good thing.
COFFEY, Q.C.:
Q. Commissioner, if we can come back and -
THE COMMISSIONER:
Q. Lunch break.
COFFEY, Q.C.:
Q. - take it up after lunch, thank you.
THE COMMISSIONER:
Q. Meet again at 2:10.
COFFEY, Q.C.:
Q. Thank you, Commissioner.
(ADJOURNED FOR LUNCH)
THE COMMISSIONER:
Q. Please be seated. Mr. Coffey.
COFFEY, Q.C.:
Q. Thank you, Commissioner. Good afternoon, gentlemen. Exhibit P-3367? Now, Mr. Hewlett, this is a document you were just shown the cover page of earlier today of the review on October 3rd, 2008, the visit you made to the James Paton Memorial Hospital in Gander, Newfoundland.
MR. HEWLETT:
A. Uh-hm.

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COFFEY, Q.C.:
Q. And the introduction is the same, other than the reference to the fact that it occurred on October 3rd.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. It's the other reports we looked at and then under "Fixation" you have noted here, in particular portions of this, "Observation of the specimen receiving area, specimen triage and the grossing of the specimens along the review of documentation leaves me to believe that the issue of fixation is being partly addressed in principle. Specimens from the OR and outlying small hospital and satellite clinics are delivered on a regular daily schedule. Breast samples are delivered immediately on procurement and lab staff is notified." You note that "breast requisitions are date and time stamped as to procurement and time received by the lab. Other specimens are not handled in this matter. It would be my recommendation to apply the same date and time stamping procedures to all specimens."

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MR. HEWLETT:
A. Correct.
COFFEY, Q.C.:
Q. You say "The specimens procured after hours are placed in a fixative and stored at room temperature until the next day. This is suboptimal. If the specimens are small, one centimetre in the largest dimension, they are best placed in formalin and fixed at room temperature. If the specimens are larger, then the fresh tissue should be refrigerated and the pathologist on call should be notified to deal with them as soon as possible." So in relation to that, I take it that in, after hours, as it were, Mr. Hewlett, you would feel that the tissue should be put in the refrigerator, the pathologist brought in, do the grossing -
MR. HEWLETT:
A. That would be correct, yes.
COFFEY, Q.C.:
Q. - at the time, the breadloafing as applicable.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:

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Q. And then placed in formalin to be fixed overnight.
MR. HEWLETT:
A. Exactly.
COFFEY, Q.C.:
Q. It goes on, "The fixation time of most specimens is now 24 hours or longer with the exception of a few rush specimens. Pathologists are preparing specimens in such a manner as to optimize fixation prior to further grossing." And it take it that that's certainly once the pathologists have it in their hands there.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. You go on to say, you speak about "The procurement time date and time receipt in the lab, time in the fixative for fresh breast specimens, date and time of grossing are all recorded. This information provides documentation is available to users of the tissue block for all future studies. This should be extended to include all specimens."
MR. HEWLETT:

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A. Correct.
COFFEY, Q.C.:
Q. Widen the scope.
MR. HEWLETT:
A. Again for obvious reasons.
COFFEY, Q.C.:
Q. And here you do then, in effect, you note that "in addition to the date and time of tissue processing is subsequently documented and may ultimately be used to determine total fixation time" and you note "that this is in compliance with the existing Canadian Consensus Guidelines and the soon to be published guidelines by the Ad Hoc committee." And then you've got a similar reference to the 10 percent buffer formalin applies provincially. Here towards the bottom here of this section, you've written, "All grossing is performed by the pathologists, assisted by a technologist. CAP check list are used for various specimen types for inclusion in the synoptic reporting format. Special instructions for the technologists are directly communicated and documented on process worksheets. In addition, diagrams are used as necessary. The

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technologist reports only occasional problems with tissue thickness. These occasional problems are immediately brought to the pathologist's attention." I take it you understood he, it's addressed -

MR. HEWLETT:

A. I actually observed that point, the technologist was along side the pathologist during grossing and there was a constant interaction between the two, so if a piece was a little too thick, the technologist would say that's a bit thick.

COFFEY, Q.C.:

Q. And it would be remedied?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. Then there's under "Processing" you've noted in relation to James Paton facility, "There is some evidence that an occasional intermittent problem exists with the processing of the tissue blocks. A random review of large blocks in the storage files found only occasional blocks that showed evidence of inadequate processing. The tissue in these

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blocks was retracted from the surface and dry." And I take it then, that this is similar to what you had found in Corner Brook, it's the same situation?

MR. HEWLETT:

A. It is, it is. And you would probably find that in just about any histology lab you go to, the occasional large tissue based -

COFFEY, Q.C.:

Q. And to tell how prevalent it was or wasn't, you'd actually have to do, actually go through quite a number of slides.

MR. HEWLETT:

A. Go through a number of those -

COFFEY, Q.C.:

Q. Record the number of blocks historically.

MR. HEWLETT:

A. Yes, yes.

COFFEY, Q.C.:

Q. And in the circumstances that wasn't actually your role to audit the past work?

MR. HEWLETT:

A. No, but I did go through maybe six cabinets.

COFFEY, Q.C.:

Q. Random sampling.

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MR. HEWLETT:

A. Just random sampling.

COFFEY, Q.C.:

Q. And this was, then had extended, these observations weren't confined to any one year, it was a general problem. Another artifact observed, rarely in a few blocks it was a very evident interface line separating the tissue and the surrounding supporting paraffin. This can occur if the tissue is allowed to cool or is drained of molten paraffin before being placed in the mold during the embedding process." Which is similar to -

MR. HEWLETT:

A. The same thing.

COFFEY, Q.C.:

Q. Same thing. And on the top of the next page under "Processing", you noted here, "a review of the schedule used on the processor showed there is an inadequate number, only two, of final alcohols in the dehydration sequence. The sequence is 60 percent, 80 percent, 90 percent, 95, percent and 100 percent. There are also only xylene changes. It is recommended that the sequence be changed to

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match these suggested sequences for the St. John's laboratory. Appendix One".

MR. HEWLETT:

A. That could easily be accommodated because they had two formalins at the front end and they're not achieving anything. Fixation has already occurred. You need one formalin container on the processor as a holding vat until the process starts. So rather than waste that space, simply moving everything down and putting another hundred in, you would essentially fix the problem.

COFFEY, Q.C.:

Q. Another hundred alcohol.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And you then go on to refer to, "I observed that the racks loaded in the processors had the organized cassettes appropriated packed. The technologist reduces the number of cassettes in each compartment of the rack from ten to eight." So in Gander, they actually had already adopted the practice that you were suggesting in Corner Brook and St. John's?

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MR. HEWLETT:
A. The technologist is already on top of it, yeah.
COFFEY, Q.C.:
Q. You go on to note, "Documentation of the processors, scheduled maintenance and reagent changes was available and indicated that this had occurred within the specified time limits. It is my opinion that frequency should be increased slightly since I detected a presence of xylene in a third and fourth waxes. Under normal usage, these two waxes should be free of xylene contamination. This and a lack of a third 100 percent alcohol in a sequence could be causes of the occasional inadequate processing" that you had observed in the blocks.
MR. HEWLETT:
A. Yes. The frequency of changes is dependant upon the load going through, you know, so they need to adapt slightly by increasing the frequency. So if they change very fifth day, once a working week, then they need to change every fourth day, probably would take care of the issue. But it does depend on the load,

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the daily load.
COFFEY, Q.C.:
Q. And it goes on to say, "The embedding centre in use had an empty headed holding well for the specimens. I recommend that the embedding centre holding well be filled with liquid paraffin to hold all specimens during embedding. This will prevent the blocks cooling and liquid paraffin draining from the tissues. Maintenance of the liquid paraffin phase of the outside tissue surface during embedding will also prevent separation and interfaces forming between tissue and its supporting paraffin." You wanted the paraffin bath, as it were.
MR. HEWLETT:
A. Common theme.
COFFEY, Q.C.:
Q. Common theme. You go on to say, "At the microtome work station, it was noted that following section pick up on slides, the mounted cross sections were dry prior to staining in a domestic microwave oven. This includes sections that are cut to be sent out for IHC. This is of concern for IHC since

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antigen degradation occurs more rapidly during a transport of sections following high temperature exposure. The reference IHC lab should be informed of this practice. Their recommendations regarding section handling should be followed. It would be preferable to simply air dry IHC sections and allow the reference lab to dry them just prior to staining. Even more preferable would be to ship the blocks to the IHC lab for cutting." I take it this is a similar thing to the hundred degree celsius, except this is a microwave?
MR. HEWLETT:
A. Except it's again, more dangerous because microwaves are not uniform in their heating. They hot spot, so some areas of the section can be tremendously overheated, while other areas have not reached the adequate temperature to stick on. In any case, CLSI documents, there is one specifically on the use of microwaves and they absolutely say do not use domestic kitchen appliances. And they're not scientific instruments, they're completely uncontrolled. It's possible to

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obtain scientific microwaves intended for these purposes. They are a lot more expensive.
COFFEY, Q.C.:
Q. And you concluded by saying, "The use of domestic appliances in laboratories is to be discouraged. These appliances are uneven and uncontrolled in their heating pattern. Only laboratory graded instruments should be considered", which is the point you just made, and then you speak about manuals and documentation, "The histology laboratory policy and procedure manual was briefly reviewed. Although not in CLSI format, the older type of procedure manual covered most basic technical procedures. A complete rewrite of this manual to current accreditation standards would take considerable time, effort, and require substantial additional resources. In addition, an overall laboratory quality system would need to be in place. This would be required if accreditation were to be pursued". It's a similar comment to Corner Brook.
MR. HEWLETT:

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A. Yes.
COFFEY, Q.C.:
Q. "There is evidence of the use of this manual, the staff is aware of the manual, and has also demonstrated their knowledge through application in several situations during my visit to the site. There is evidence of some QC documentation throughout the work processes. A more complete documentation would be valuable, for example, a microtomy worksheet with corrective actions taken. The pathologists check the control slides for H & E and special stains, but no record or corrective action documentation is kept. One of the most important QC checks in histology occurs at the H & E staining bench. Slides and blocks should be brought together for comparison after staining to ensure a complete section of the correct tissue is on the slide. This QC check is neither being performed nor documented at this time. The technologists do check the section for completeness during microtomy, and that is appropriate. However, it is the check after staining that is more important", and you go on then, "There needs

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to be sign off sheets at all of the workstations signing ownership and responsibility for the task. Where possible, the specific case numbers should be listed. Corrective action records sheets should also be in use at the same workstation. The technologists are responsible for checking the quality of cutting and staining, together with troubleshooting and documenting any required remedial action", and I take it then that in Gander in the hospital there, there needed to be more paperwork associated with that process?
MR. HEWLETT:
A. And again outside of St. John's that was a common theme.
COFFEY, Q.C.:
Q. Okay. They needed more paperwork in recording actually what the QC -
MR. HEWLETT:
A. More QC documentation.
COFFEY, Q.C.:
Q. And assuming that they at some point have the QC documentation, you noted, "An overall QA use of QC information is not evident. Viable

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information needs to be collected and used to take corrective action throughout their processes in order to reduce the occurrence", and I take it this is the same thing, get the QC documents and then utilize them for QA?
MR. HEWLETT:
A. Uh-hm.
COFFEY, Q.C.:
Q. Your reference to staffing in Gander, I take it, is a similar reference to the one you had made to -
MR. HEWLETT:
A. Very similar.
COFFEY, Q.C.:
Q. To Corner Brook, and under summary, "There has been a real effort in the front end of the histology lab to determine the best patterns of practice and implementation of these practices. Fixation time and related tissue sample thickness is just one application of this. This quality activity needs to be expanded to all areas of the histology lab". So I take it, you're saying, look, on fixation, and tissue thickness going in the cassettes -

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MR. HEWLETT:
A. Yeah.
COFFEY, Q.C.:
Q. The work is being done, but that sort of approach to QC should be expanded into histology generally?
MR. HEWLETT:
A. Exactly. The other issue that is there is that the technologists are not doing the examination of the stains. It's part of the technologist duties to do that, and to do the appropriate documentation.
COFFEY, Q.C.:
Q. And that is, I take it, the issue of the technologist reading the control slides, the external control slides?
MR. HEWLETT:
A. Absolutely, but even for H & E, how can one assess the staining unless one actually assesses it, you know.
COFFEY, Q.C.:
Q. So your observations outside St. John's in relation to the H & E stained slides was what, who was examining it?
MR. HEWLETT:

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A. Some places, the technologists were doing it. In this particular instance, the pathologist was doing it.
COFFEY, Q.C.:
Q. And it's your view that the technologist should be doing it?
MR. HEWLETT:
A. Oh, yes, absolutely.
COFFEY, Q.C.:
Q. The pathologist may do it too, but you -
MR. HEWLETT:
A. Well, he can do it later, but before they go out, they need to be examined. That's how one determines if there needs to be changes made on a staining machine, replenishment of staining solutions and so on. You have to check the QC. You know, you just don't a whole day's work and then send it out and have the pathologist come back and say the stains are not working.
COFFEY, Q.C.:
Q. And compliance, you noted, "I believe that the laboratory's efforts to date in regard to the handling of fresh breast specimens", and you go on from there. You make a similar comment

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here in terms of compliance with the Canadian Consensus Guidelines for HER2/neu testing.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. ASCO CAP for HER2/neu testing, and the Ad Hoc Committee.
MR. HEWLETT:
A. Yes. I deliberately put that emphasis on because of the nature of the Commission. It's important to get it right for breast, but it's also to get it right for everything else, but there are guidelines in existence for at least part of the breast markers, the HER2 marker, Canadian guideline that can be widely applied across to ER.
COFFEY, Q.C.:
Q. If we could, please, Exhibit P-3368. Now, Mr. Hewlett, this is your visit to the Charles S. Curtis Memorial Hospital in St. Anthony. I'll refer to it as the St. Anthony Hospital. On the second page, you begin by saying, "A review of Curtis Memorial Hospital, pathology laboratory, was conducted on October 6th p.m. and 7th a.m, 2008. The review was a process

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of observation, questioning of technologists. Unfortunately, the pathologist was away", and I understand Dr. Dankwa happened to be in Europe at the time?
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. "An examination of the resulting product at each of the different work areas in the histology lab, particular attention was directed to the pre-analytic processes used to prepare a tissue specimen for sectioning prior to staining and examination", and you note that "the histology laboratory policy and procedure manual was briefly review. Based on the contents of the existing manual, a number of questions were developed to ask the staff, and you found the staff there again very - technical staff very enthusiastic and forthright in their answers and dedicated to what they're doing. Here under fixation, Mr. Hewlett, you've written the following, "Observation of the specimen receiving area, specimen triage, and the grossing of the specimens, along with the review of

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documentation, leads me to believe that the issue of fixation has only been partly address in principle. A new fixation policy has been written, but has not yet been implemented since certain unique and difficult physical circumstance apply. Specimens from the hospital OR are received on a regular basis throughout the day. Requisitions are date and time stamped as to procurement and time received at the lab. Breast samples are delivered immediately on procurement and lab staff is notified. Either the pathologist, or in his absence, a trained technologist will slice the tissue at appropriate intervals and insert formalin soaked paper towels and immerse the specimen in an appropriate volume of fixative for a minimum of 24 hours", and you go on to say, "Specimens procured after hours are placed in fixative and stored at room temperature until the next day. This is sub-optimal", and you then talk about if there's small, they're best placed in formalin, but if they're - fixed at room temperature, but if they're larger, the fresh tissue should be refrigerated and the

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pathologist, in this case, Dr. Dankwa, should be brought in to deal with it.

MR. HEWLETT:

A. There are additional problems here.

COFFEY, Q.C.:

Q. In St. Anthony -

MR. HEWLETT:

A. If he's not there, then somebody has to be notified and called to deal with it.

COFFEY, Q.C.:

Q. Now in relation to that, Mr. Hewlett, because you've noted here that a trained technologist in the pathologist's absence will slice the tissue at appropriate intervals, insert formalin soaked towels and so on for breast samples -

MR. HEWLETT:

A. Uh-hm.

COFFEY, Q.C.:

Q. So I take it that the technologist who is there is trained - at least you understand is trained to do this for breast?

MR. HEWLETT:

A. I understand, but I didn't observe that.

COFFEY, Q.C.:

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Q. But you understood that was so?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And from your perspective then, might the same thing be done for other tissue?

MR. HEWLETT:

A. Oh, absolutely, as long as they are appropriately trained.

COFFEY, Q.C.:

Q. Yes.

MR. HEWLETT:

A. I did note there was some reluctance from some of the technologists who rotate through the department. The technologist that is trained is in there more or less every day, but some of the others rotate through. There is some reluctance to do things for which they are not appropriately trained and feel competent, and one can only admire that, that is the appropriate professional attitude to have. So if this one technologist is away and the pathologist is away, then, of course, we have the problem again.

COFFEY, Q.C.:

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Q. And here - this is, I gather - this paragraph deals with a situation that St. Anthony, in fact, because of its geographic location, finds itself in, and its service area, you've written, "Specimens from Labrador City and Goose Bay are placed in fixative and delivered on an irregular daily schedule depending on the availability of transport. This is appropriate for small, less than 1 centimetre thick specimens, but completely unacceptable for larger specimens, including breast. The larger specimens need very large containers of fixative and weigh a considerable amount when appropriately packaged for air shipment. Arrangements will have to be made to train appropriate personnel at these locations to slice the larger tissues appropriately, fix them for the correct period of time, and then place the fixative - I'm sorry, then replace the fixative with a smaller amount for shipping".

MR. HEWLETT:

A. After fixation is complete, one doesn't require the same volume.

COFFEY, Q.C.:

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Q. After the 24 hours.

MR. HEWLETT:

A. They need to be kept wet.

COFFEY, Q.C.:

Q. Yes.

MR. HEWLETT:

A. But after the 24 hours, you can used a reduced volume for shipping purposes, and there are regulations about that. They need to be in double containers which are leak proof, and the second container must be able to contain the volume of the first container if it breaks, so on and so forth. Some of these specimens can really get quite large. We're talking, you know, 10 litres of fixative. That's essentially a five gallon pail.

COFFEY, Q.C.:

Q. Yes, and you conclude by saying, "This will invariably prolong fixation past the recommended 48 hours in the fixation policy adopted from St. John's. The policy will need to be rewritten to accommodate these lengthened fixation times". That would be in relation to the ones coming out of Labrador?

MR. HEWLETT:

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A. Yes, if the plane doesn't fly or if it's full, they just leave them behind.
COFFEY, Q.C.:
Q. And -
MR. HEWLETT:
A. I don't believe that to be an issue, by the way. I think the guidelines are incorrect. The ASCO CAP guidelines set 48 hours maximum. The Canadian guidelines set 72 hours, but do comment that longer than that will not exclude the sample from testing.
COFFEY, Q.C.:
Q. And here in the third paragraph on page three, you've written, "In addition, the date and time of tissue processing is subsequently documented and may ultimately be used to determine total fixation time. This is in compliance with existing Canadian Consensus Guidelines and the soon to be published guidelines by the Ad Hoc Committee". You note "prolonged fixation times exceeding 72 hours will not meet the Ad Hoc Committee on ER testing guidelines, but will meet the Canadian Consensus Guidelines for HER2/neu testing".
MR. HEWLETT:

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A. Uh-hm.
COFFEY, Q.C.:
Q. Could you elaborate on that a little bit for the Commissioner?
MR. HEWLETT:
A. Well, there again the Canadian Consensus Panel had the vision to realize that the 48 hour limit has to be malleable. There are long weekends and long, long weekends, and some institutions are not staffed. There is no scientific evidence that states that 48 hours is the upper limit and, you know, thou shalt not pass this barrier. ASCO CAP guidelines quite categorically state no more than 48 hours. The Canadian guidelines adapted that to be a little more realistic. It would be possible to exceed the 72 hours as well in certain circumstances. So the Canadian guidelines suggests that that's okay, and does not prevent testing from occurring. It does mean the laboratory needs to know this, however, so that they can make any adjustments to antigen retrieval if they're required.
COFFEY, Q.C.:
Q. And that is the IHC lab would have to know?

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MR. HEWLETT:
A. Yes, they should know this, anyway. I mean, the guidelines also suggest these times should be on the reports, the final surgical reports.
COFFEY, Q.C.:
Q. And here in this section, you conclude by saying, "Complex specimens is performed by the pathologist, assisted by a technologist. When the pathologist is away, the large specimens are shipped out of the province. The technologists grosses small simple specimens. The CAP checklist are used for various specimen types for inclusion in a synoptic reporting format. Special instructions for the technologists are directly communicated and documented on process worksheets. In addition, diagrams are used as necessary. The technologist repots some problems with tissue thickness. These problems are immediately brought to the pathologist's attention". I take it that was what the technologist was telling you?
MR. HEWLETT:
A. Yes. The other issue here is - let's say something comes from Labrador City

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unbreadloafed. It then arises (unintelligible) and if the pathologist away, it will then get shipped somewhere else unbreadloafed.
COFFEY, Q.C.:
Q. In fact, if it comes from Labrador City unbreadloafed and it actually takes, for example, 24 or 48 hours to get down, unbreadloafed, I take it, for the same reason that it's a problem to leave it in the OR overnight in formalin, the same problem applies?
MR. HEWLETT:
A. It's essentially toast.
COFFEY, Q.C.:
Q. Yes, and -
THE COMMISSIONER:
Q. Excuse me, before we go on, Mr. Parks, does your laboratory receive any samples or specimens from Northern Ontario, and do you have that kind of problem?
MR. PARKS:
A. No, we don't receive any from Northern Ontario. We receive just from hospitals in our area, but to address this very problem,

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our pathologists went to some smaller hospitals, met with the surgeons who actually were doing the surgery, taught them how to breadloaf the breast, and the surgeons were more than happy. They now after their surgery, go to the table, breadloaf the breast tissue, put it into the fixative and then it gets shipped to us. It can take overnight to get to us, and it's not an issue.

THE COMMISSIONER:

Q. So your solution was to make use of surgeons?

MR. PARKS:

A. Absolutely.

THE COMMISSIONER:

Q. Thank you.

COFFEY, Q.C.:

Q. Now here, you go on then to speak about processing, Mr. Hewlett, and you say "there is evidence that an ongoing problem exists with the processing of the tissue blocks," and this is again, you "performed a random review of the large blocks in the storage files prior to June 2008."

MR. HEWLETT:

A. That date because at around that time they got

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a new processor, so I also looked at.

COFFEY, Q.C.:

Q. "Found numerous blocks that showed evidence of inadequate processing. The tissue on these blocks was retracted from the surface and dry," I'm sorry, "in some cases, the retraction was severe. This is indicative of tissue that was insufficiently dehydrated, cleared and/or infiltrated with paraffin. I did find a few blocks containing smaller pieces of tissue that showed similar inadequate processing. This indicates the larger tissue blocks were likely too thick to be adequately processed by the routine processing schedule. Examination of tissue blocks prepared since June 2008 when the new tissue processor was installed also found a number of large tissue blocks showing evidence of inadequate processing. Observation of the technologist during grossing of small specimens showed the appropriate selection of tissue thickness being placed in cassettes." So I take it what you were seeing when you were there was it was thin enough, being cut thin enough?

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MR. HEWLETT:

A. When I was there, and the earlier stuff, of course, who knows, and I suspect even from-- when I comment that the retraction is severe, I really mean severe. Sometimes there's sort of a deep well and the block is sunken back so badly, and that's often indicative of tissue that was not appropriately fixed either. Can't swear to it. There's no real way to know until I asked to see some of the H & E slides and they were, in fact, pulled and I had a quick look, but couldn't determine much because the microscopes are completely useless. I'm sorry, but they're -

COFFEY, Q.C.:

Q. Yes, well, that's -

MR. HEWLETT:

A. - they are in such bad shape. They're unusable, and I went down to the microbiology lab, where of course, it's essential that they have a working microscope and the senior technologist in there was so frustrated because it wasn't working and she was trying to examine some slides. So I tried to fix it for her the best I could, but it was still

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terrible.

COFFEY, Q.C.:

Q. I'm going to come back to actually what happened in Gander, in terms of the day. I took you through Corner Brook. I didn't take you through Gander. I'm going to take you through, as well, St. Anthony, and going to come back to that point. I'll finish this and then come back through, your actual activities in those two locations.

You've also said here, "another artifact observed rarely in a few blocks was a very evident interface line, separating the tissue and the surrounding supporting paraffin," and this is the same issue about lack of molten paraffin?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. And then, Mr. Hewlett, you said "review of the schedule used on the processor showed that there is an inadequate number of graded alcohols in the dehydration sequence. The sequence is 70 percent, 80 percent, then a jump to 100 percent. There are also only two

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changes of the xylene substitute, Safe Clear II. This new processor also only allows three paraffin wax changes. It is recommended that the sequence be changed to match the suggested sequence for the St. John's lab."

MR. HEWLETT:

A. With the exception of the fourth wax.

COFFEY, Q.C.:

Q. Fourth wax, that would only be three possible.

MR. HEWLETT:

A. Yeah.

COFFEY, Q.C.:

Q. And "it was noted that a xylene substitute Safe Clear II was being used for the clearing process. Although in itself use of such substitutes may be a more ecologically friendly approach," this is the same comment you'd made about xylene substitute elsewhere?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. Same substantial comment.

MR. HEWLETT:

A. And this is exactly the same comment for the same reasons.

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COFFEY, Q.C.:

Q. Just a different substitute.

MR. HEWLETT:

A. Different substitute, yeah.

COFFEY, Q.C.:

Q. You noted, "I observed that the racks loaded in the processors had the organized cassettes appropriately packed and that this processor rack was fitted with coil wires to separate cassettes. By providing more space between the individual cassettes, this ensures superior reagent flow around the tissue. The staff is still able to maintain the order of the cassettes in a rack, an excellent QC practice." So this one, there was appropriate spacing then of the cassettes?

MR. HEWLETT:

A. Oh absolutely, and this particular instrument comes with--it looks like a Slinky, that fits into the compartment and the coil wires are about a millimetre thick and it keeps each cassette separated by an appropriate amount. This is the ideal kind of processing rack.

COFFEY, Q.C.:

Q. And here, you go on to say, "documentation of

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the processor's scheduled maintenance and reagent changes was not available as a hard copy. Instead, the instrument log records this information electronically. Examination of the instrument log indicated that this had occurred within the specified time limits. It is my opinion that the frequency should be increased slightly since I detected the presence of Safe Clear in the third wax. Under normal usage, the second two waxes should be clear of--should be free," I'm sorry, "of clear and contamination." In effect, the same thing as the xylene, same -

MR. HEWLETT:

A. Yes. It's a little worse, because Safe Clear is a slower clearant and will be slower to eradicate from the waxes.

COFFEY, Q.C.:

Q. And can that have any effect--it remaining in the waxes, if there's too much of it in the wax and it remains in the wax, can that have an effect on the tissue?

MR. HEWLETT:

A. Exactly the same as we previously discussed, yeah.

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COFFEY, Q.C.:

Q. And "the instrument has facilities for connection of an electronic data storage device to store backed up data, and hence a print out may be obtained of the process log. I recommend that these facilities be used." I take it, in other words, that they use the ability to back it up?

MR. HEWLETT:

A. When they got the processor, there is no data--there is no storage device for the data log, and the technologist wasn't sure whether that had been ordered and was delayed or whether it was ever going to come. But they are expecting a second machine and so they will be in contact with the company and can obtain appropriate recording devices. If there's a power out, all your QC data is gone, and that's why it's important to back it up to a disk and/or print it out.

COFFEY, Q.C.:

Q. I was going to ask you about that whole idea of backing up data, okay. So data that's stored electronically, and there's a certain amount of it certainly done now and arguably

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into the future, perhaps even more so.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. You think laboratories should routinely back up electronic data that they capture in machinery?
MR. HEWLETT:
A. Absolutely. Either that or get a hard print out.
COFFEY, Q.C.:
Q. Or perhaps both, if you got the paper.
MR. HEWLETT:
A. Or perhaps both, yeah.
COFFEY, Q.C.:
Q. I'm going to ask Mr. Parks this question, because you're still involved day to day in an active lab. What is your lab's approach to maintaining or keeping track of electronic data like coming off of, for example, a DAKO machine, that's in a DAKO machine?
MR. PARKS:
A. We run a hard copy after a run and store the hard copy.
COFFEY, Q.C.:

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Q. Okay, so that's the way it's dealt with is you print it out and store that.
MR. PARKS:
A. That's how we deal with it. We store the hard copy, yes. The stuff from our routine running of the regular computer system, of course, that is backed up onto tape and stored forever, but that's the whole great big lab operation system. But on the smaller instruments, we run a hard copy and store it.
COFFEY, Q.C.:
Q. How long has that been the practice?
MR. PARKS:
A. Well, since we've had our machines, we probably have it in storage somewhere we have to--Ontario requires that we maintain these records for a certain period of time, and it's held in storage in a room off in another building.
COFFEY, Q.C.:
Q. Now do you use a DAKO autostainer?
MR. PARKS:
A. We have a DAKO for immuno, yes.
COFFEY, Q.C.:
Q. Immuno. Do you know if there's a computer

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used with it?
MR. PARKS:
A. There is a computer attached to it, yes.
COFFEY, Q.C.:
Q. And do you know, do you have any familiarity with whether or not that computer kind of keeps track of the runs, all the runs today and tomorrow and the next day?
MR. PARKS:
A. Oh yeah. You can go into it and see--because when you enter in, you enter in the date and stuff as you start the run, and at one point, we had to actually have it downloaded because our drive, after five years, got so full. It's all in onboard, every run and the solutions and everything are onboard, yeah.
COFFEY, Q.C.:
Q. And when that happened, you say downloaded, was it captured electronically?
MR. PARKS:
A. I was not in charge at the time. I believe it was, but I do know we have it all on hard copy.
COFFEY, Q.C.:
Q. Okay, you have it on hard copy.

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MR. PARKS:
A. The exact same data that's stored in there is what we print out daily and attach to our daily worksheets, which are stored indefinitely.
COFFEY, Q.C.:
Q. At the top of the page five, Mr. Hewlett, you've said--you speak about the embedding centre, and you said "an empty heated holding well for the specimens" and this is when you're looking for the liquid paraffin bath, as it were.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. And you then say the following "the laboratory has some new instrumentation with more apparently on the way, although how they will accommodate it in such already skimpy quarters is difficult to understand. The cramped, disorganized, non-ergonomic and frankly, unsafe, existing working environment of this histology lab needs to be rectified urgently." I take it that's your view that there's not enough space?

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MR. HEWLETT:
A. I was just horrified that people should be working under these circumstances. There was a--the grossing room is a little alcove just off it. The odour of formaldehyde in that room was almost overpowering, even to my sense of smell. That's simply not appropriate. The processing machine is placed so close to the cutting bench that the technologist has to sort of sidle in sideways and if they back up from the microtome, as she did in one instance, and actually broke the door, the plastic door of the processing machine, by crashing into it. It's important that there be a safe escape from a microtome should you drop a knife or something like that. You certainly don't want it running in your lap. These are severe safety issues. Cutting sections is a dangerous occupation. There should be a clear path of escape.

There's multi use of the benches so that, you know, there's staining occurring on the same bench as section cutting and everything is piled on top of each other. There are potentially two people working in there. I

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spent a lot of my time out in the corridor talking to them through the door, just so I wouldn't be in their way. My view, this is a very dangerous working environment.

COFFEY, Q.C.:
Q. The one in St. Anthony.

MR. HEWLETT:
A. They're supposed to be renovating it, but I think that it's been underway for some considerable time. The ventilation system in the main lab is not working and twice while I was there, the supervisory technologist contacted maintenance to see if they could do something about it. This is part of the overall quality of the laboratory.

COFFEY, Q.C.:
Q. Yes. Here, you go on, you speak on about manuals and documentation. You say "the histology laboratory policy and procedure manual was briefly reviewed. Although not in CLSI format, the older type procedure manual covered most basic technical procedures. A complete rewrite of this manual to current accreditation standards" again would require considerable time and effort and they would

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need to do that if accreditation is going to be pursued. "There is evidence of the use of the manual. The staff is aware of the manual and has also demonstrated their knowledge through application in several situations during your visit to the site. There is evidence of some QC documentation throughout the work processes and more complete documentation would be valuable, for example, a microtomy worksheet with corrective actions taken.

The technologist checks the control slides for H & E and special stains. Documentation is kept in Meditech. This is an onerous task, given that the only microscope in the lab has a broken lamp housing, making it impossible to adjust for correct illumination. It also has insufficient objectives of the wrong magnification and is essentially unusable. The technologists are responsible for checking the quality of cutting and staining, together with troubleshooting and documenting any required remedial action. It is hard to perform that task with inadequate equipment. A new

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instrument is necessary."

You go on to say "one of the most important QC checks in the histology occurs at the H & E staining bench where the slides and blocks are brought together for--they should be brought together for comparison after staining to ensure that a complete section of the correct tissue is on the slide. This QC check is neither being performed nor documented at this site"--I'm sorry, at this time, in St. Anthony, it would be.

"There needs to be sign off sheets at all of the workstations assigning ownership and responsibility for the task. Where possible the specific case number should be listed. Corrective action record sheets should also be in use at the same workstations. An overall use of QC--QA use of QC information is not evident," and I take it then this relates to the idea of utilizing QC for QA purposes?

MR. HEWLETT:
A. Absolutely.

COFFEY, Q.C.:
Q. You've noted here that--you've said here "valuable information needs to be collected

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and used to take corrective actions throughout the process in order to reduce the occurrence. The QA processing of the QC information, the troubleshooting and the ultimate corrective action should be assigned to a senior technologist position in the lab." I take it your sense was -

MR. HEWLETT:

A. That's because of the rotating staff. It's a relatively small hospital. I understand that, but there needs to be consistency.

COFFEY, Q.C.:

Q. I'm going to get to that. I'm going to come back to this in the staffing. "The entire laboratory requires an updated quality assurance system, hospital administration needs to address this and provide resources appropriate to the importance of a quality regional laboratory service."

And under staffing, you've written the following, "histology is a lab discipline that requires very specific skills that need time and practice to develop and hone. Only one technologist spends the majority of their time in histology. The other technologists rotate

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through all departments of the lab. The current staffing levels appears to be barely adequate for the workload. The technologists feel out of the loop and that they don't matter. The role of the technologist should be expanded to encompass all QC and QA activities. Continuing professional development for the pathologists and technologists requires more resources allocated and participation encouraged. It is also not too early to be developing a succession plan."

So in relation to St. Anthony, what was the situation there, Mr. Hewlett, in terms of the staffing?

MR. HEWLETT:

A. They were short staffed basically. As you can imagine, I spoke with the supervisor of the laboratory and there's some difficulty in getting people to go there, of course. How they're going to address that, I'm not sure. But certainly, having a working environment in that sort of shape is not attractive to have people want to go work at. The laboratory staff are trying and have bene trying for some

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time to improve matters. They are acutely aware of their deficiencies in quality control and assurance, and really expressed a desperate desire to do something about it, but there are no resources being allocated.

COFFEY, Q.C.:

Q. And here, under summary, you've said "there has been some effort in the front end of the histology laboratory to determine the best patterns of practice and implementation of these practices. Fixation time and the related tissue sample thickness on site is just one application of this. The more difficult task relating to fixation at the distant sites still has to be addressed. This quality activity needs to be expanded to all areas of the histology lab and to the lab in general. The technologists all expressed enthusiasm and genuine eagerness to learn about the rationale behind the latest practices and techniques of tissue handling that are so necessary to accommodate ancillary testing methodologies such as IHC," which is what you were just referring to.

And then finally, under compliance,

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you've said "I believe that the laboratory's efforts to date, in regard to the handling of fresh breast specimens, fixation policies/procedures and grossing practices does not yet place them in compliance with the important pre-analytic portions of the Canadian Consensus Guidelines for HER2/neu testing, the ASCO CAP guidelines for HER 2 testing and the soon to be published ad hoc committee ER testing guidelines. With further modifications to the tissue processing and embedding protocols correcting any potential remaining processing insufficiencies, validation of the use of a xylene substitute and consultation with the IHC lab regarding other aspects of tissue preparation" which I take it is the ones involving more than 48 hours fixation possibly?

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. "The effects of poor tissue preparation on IHC testing will be minimized". And then here again you have a suggestion for the processing.

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Now, Mr. Hewlett, I'm going to ask you then, because I've taken you to Corner Brook on the 2nd in terms of you'd arrived in Corner Brook and going through your day. Perhaps you could kind of pick us up then, take us through--and bearing in mind, we've looked at the report from Corner Brook, but things we haven't touched on in Corner Brook, if anything.

MR. HEWLETT:

A. I spent some time with the pathologists, three of the four, and the impression I got was that they eager and anxious to, as they put it, get it right. They needed some guidance and they had the fixation policy from St. John's and have implemented it with the exception of the putting fixed stuff in the fridge. The technical staff were also extremely eager and they were working hard to improve their quality control documentation and so on. And again, were very willing to want to run a quality system. That was the overall impression in Corner Brook.

COFFEY, Q.C.:

Q. Any other observations from Corner Brook, in

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particular?

MR. HEWLETT:

A. Apart from the heating of the slides which are -

COFFEY, Q.C.:

Q. That's--you've already referred to, I think.

MR. HEWLETT:

A. - (unintelligible) formalin, I think, this is a bit inappropriate. The reason they're doing that is because the automatic staining machine was causing slides to come off. And so they increased the heating to try and get them to stick on. They have a new staining machine with onboard drying which may help somewhat, but that still leaves slides for immunohistochemistry and special stains to be dried.

COFFEY, Q.C.:

Q. Gander, could you tell us about your visit to Gander?

MR. HEWLETT:

A. Gander was very interesting. Both pathologists there were extremely eager to, you know, again, do the right thing, so to speak and were interested in how other people

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were handling this. The technologists, they have really good interaction. The technologists there for most of the day, really interacts well with both pathologists. So, that's very good. I would like to see, you know, the responsibilities for some of the quality control, particularly in terms of staining, passed back to technologists where it belongs, but again, overall, that was--it was a consistent theme wherever I went that the people involved really wanted to get this right.

COFFEY, Q.C.:

Q. And St. Anthony, your visit to St. Anthony, because you were there--you flew up, you were there in the afternoon and then the next morning.

MR. HEWLETT:

A. The afternoon and the following morning, yes.

COFFEY, Q.C.:

Q. Would you take the Commissioner through that?

MR. HEWLETT:

A. There again, it was two technologists that I got to speak to and the lab supervisor. Again, they're eager and willing and anxious,

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but under those working conditions, it's pretty difficult. They had only just become aware of the fixation policy and I understand that for the distant sites, there are some difficulty in actually implementing it at this time, but I'm sure that Dankwa will make the appropriate move there.

COFFEY, Q.C.:

Q. And you referred to the physical facility, you made your observations on that.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. You did refer to microscopes, particularly in St. Anthony.

MR. HEWLETT:

A. Yes.

COFFEY, Q.C.:

Q. It was your observation about the one in the histology lab.

MR. HEWLETT:

A. It's essentially unusable, I mean, it's a paper weight.

COFFEY, Q.C.:

Q. And that's the one that the histology

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technologist had available to -
MR. HEWLETT:
A. Check the quality control.
COFFEY, Q.C.:
Q. And then there was--you went to another part of the lab -
MR. HEWLETT:
A. Because the technologists rotate around, in microbiology, of course, they usually have a higher quality microscope. So, I went down there to see if I could use that and the senior technologist in there was practically tearing her hair out because she actually had a specimen she was trying to report on and somebody on call the previous evening had readjusted the microscope and she couldn't adjust it back. And essentially, it was--I mean, we got an image finally, but it wasn't--a quality one would have been helpful.
COFFEY, Q.C.:
Q. Now, in relation to the microscope you saw in the histology in St. Anthony, was it--the problem, as best you could tell was caused by what? Was it just lack of -
MR. HEWLETT:

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A. Oh, the lap housing was broken, it was an old, old instrument. The lap housing was broken and it was impossible to set the microscope up to actually see anything worthwhile, in fact, to see anything.
COFFEY, Q.C.:
Q. Now, in looking--you had the opportunity to look, to utilize the microscopes, I take it, at St. Clare's or some, one or more microscopes at St. Clare's -
MR. HEWLETT:
A. No, I didn't actually.
COFFEY, Q.C.:
Q. You didn't, okay. Where in St. John's did you -
MR. HEWLETT:
A. At the immuno lab. Both Bill and myself were at the (unintelligible).
COFFEY, Q.C.:
Q. (Unintelligible), yes. And in terms of that, it appeared to be functioning -
MR. HEWLETT:
A. Fine.
COFFEY, Q.C.:
Q. - fine. What about in Corner Brook?

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MR. HEWLETT:
A. I did, in fact, sit down with the pathologists and the technologists in one of the pathologist's offices to review some, actually, a couple of special stains and that seemed to be working fine.
COFFEY, Q.C.:
Q. And, if I could, Gander, I'm sorry, what was the situation -
MR. HEWLETT:
A. I'm sorry, that was in Gander.
COFFEY, Q.C.:
Q. Okay. How about in Corner Brook?
MR. HEWLETT:
A. Yeah, they had appropriate microscopes.
COFFEY, Q.C.:
Q. And appropriate, but as well, I take it, that they appeared to be -
MR. HEWLETT:
A. Functional.
COFFEY, Q.C.:
Q. - functioning, maintained.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:

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Q. In essence, maintained is what I'm asking you about.
MR. HEWLETT:
A. Yes.
COFFEY, Q.C.:
Q. Now, if we could please, bring up Exhibit P-3359? Now, as well, this is the slide presentation, Mr. Hewlett, that you prepared, I believe at my request, and it's entitled "Routine Tissue Preparation in Modern Diagnostic Histopathology". I thought it might be of some assistance to the Commissioner and others present and we had a number of such presentations. It never hurts to be again, exposed to it and to have your views, if you have some thoughts on this. If you could bring up too, please, Registrar--is this available electronically as a PowerPoint?
REGISTRAR:
Q. Yes (inaudible).
COFFEY, Q.C.:
Q. There we are. Mr. Hewlett, I'm going to leave this then in your hands.
MR. HEWLETT:
A. Do I have control of -

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COFFEY, Q.C.:
Q. Yes, I believe you do.
MR. HEWLETT:
A. I have to say this, this is all I actually had with me on my laptop because I anticipated going home before the hearing here. It wasn't the one I intended to use for you, but it will suffice.
I'm not going to look at every slide, but I included this to indicate that we have been doing what we do for many, many years. Formaldehyde is the fixative that was introduced in 1893 and by 1899 studies had been performed looking at a whole variety of picture tubes and tissue processing processes and the decision at that formaldehyde offered the best morphological information and was the method of choice.
And so between 1910 and 1950 worldwide formalin fixation paraffin embedding became the prevalent technique for a majority of the world. Again, preparation of sections involves manipulation of the raw tissues and there are many steps involved, but the most important of these is fixation. It is the key

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to the world. There are some people who feel that with the advent of antigen retrieval, as it's laughingly called, it also overcomes poor fixation because, you know, the retrieval, the magic box will do something, nobody is sure what, but it will do something. But, in fact, it can't and I'll get back to that a little bit later. So, fixation is the key and I'm going to come back to fixation because one cannot separate that from the process. The influence of processing is again, almost entirely dependent on the quality of the fixation. Essentially we need to--70 percent of tissue is water--we need to remove that and to replace it with a medium which can be hardened, the support medium and commonly, that's wax.
If we dehydrate with alcohol, alcohol is not missable in molten wax, so we put an intermediate solvent in its place, commonly called clearing agents because they raise the refractive index of the tissue and make it go clear. And then infiltration with the support medium which is almost universally wax. There are some effects of these steps and if we

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perform them after optimal fixation in formaldehyde, ethanol for dehydration will remove some lipids and a few proteins, those that have not been immobilized, very few. And the results of this can be a very small amount of tissue dependent shrinkage. Some tissues shrink more than others. Some hardening also occurs and that's a good thing because we need something a little firmer to cut a thin section.
It will also function, ethanol, as a fixative and this is where it starts to get complicated. But as a fixative, ethanol produces tremendous shrinkage inherently right off the bat, of up to 40 percent. And a lot more hardening and a lot more removal of various proteins and things. Following dehydration, we need to use one of these intermediate solvents and the common two was xylene and toluene that can be used interchangeably. They are true clearing agents, they do raise the refractive index of the tissue, but they also remove some lipids, cause a little shrinkage and also some hardening.

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And now we can move the tissue in xylene into a liquid wax for the final infiltration. The paraffin wax itself will remove some lipids and cause some hardening, but it's the heating that causes the majority of shrinkage, okay. We can reduce this shrinkage by minimizing the heat shock on transfer from xylene to molten wax and that's one reason why I use the CI (phonetic) recommendation to raise the temperature of the solvent so that it would be less of a ten percent differential from the xylene into the hot wax. At times in these, all of these reagents may be shortened by agitation and in the case of paraffin wax, we can shorten its time by negative pressure. We pull a vacuum on a xylene, it will evaporate more rapidly and hence we need less time. The overall effects of the processing as I've briefly described are as you see on the screen. But there will always be some of this, okay, always; however, those effects will be minimized for running an optimal formality on fixation. Okay, I mean, greatly minimized. I managed to borrow this of Wikapedia, Commissioner, it's a bit blurred

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but it's all about the proteins and just a brief reminder that proteins are poly peptoids, that is chains of peptoids strung together and they are dynamic structures. The primary structure is the chain of peptoids linked together, but because of surface charges, these inherently on the go folding and the principle folding is known the secondary structure and there are many versions of this, but there is a pleated sheet and a alpha helix, are two common ones, and these can occur at various positions along the peptoid chain, depending on and they can be local, you can have many different secondary structures within a single protein. And then the tertiary structure is what happens when these folded structures start to interact with each other. The more complex folding and you can see that the protein is sort of bundling up into like a ball of wool and this again is a dynamic processing, keeps moving, it's never truly stationary and the charges on the surface keep changing and so on. And then finally we have the quaternary structure and this is what happens when the tertiary

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structure, the protein itself either interacts with another copy of itself or whether an entirely different protein, they interact and again there is structural and conformational changes. And this is key when we start talking about immunohistochemistry because it's the shape of what is comformational changes that we're detecting with the antibody or at least portions of it. So that briefly is what one of these things would look like in diamatic form if we were to string all this together, okay. I've given you this because in order to understand the nature of fixation, it's important to know what happens to these various structures. With formaldehyde, it's known as a non coagulant fixative or an additive fixative. The protein primary structures are untouched, the secondary structure is left intact, that's the initial folding and the tertiary and quaternary structures are only modified by something called methylene bridge cross-links from the formaldehyde. Most of that modification, over 90 percent of it is completely retrievable so we can restore the conformation of the

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original protein largely. There is very little loss, less than one percent of the total protein in the tissue, okay.

COFFEY, Q.C.:

Q. That's assuming it's done correctly.

MR. HEWLETT:

A. Yes. On the other hand, alcohol and there are lots of other fixatives, but this is important because we use alcohol later in the process. Alcohol is a fixative, leaves the primary structure in tact, it alters dramatically the secondary tertiary and quaternary structures and it does this by what's called a hydrophillic, hydrophobic inversion, it I can go back one, Commissioner, you'll see the core of the protein here is the hydrophobic bit. Proteins function in an aqueous environment, so they're hydrophillic water loving groups are on the outside, so that they can interact. They hydrophobic groups are tucked away inside the core of the protein. When we drop that protein into alcohol, those positions reverse and so we now have a hydrophobic outside with a hydrophillic interior and the protein promptly precipitates out of solution, the

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whole thing coagulates, sort of like dropping a raw egg into vinegar, okay, which is a fixative.

COFFEY, Q.C.:

Q. And I take it then if alcohol fixation occurs and we'll address this in a bit, somewhere in the process, the effect is that you can lose up to 40 percent of the protein because of the alcohol fixative process.

MR. HEWLETT:

A. Exactly.

COFFEY, Q.C.:

Q. And not only does it pause, but it alters the secondary tertiary structures often irretrievably, you just can't get it back, period if the alcohol gets involved, really gets involved.

MR. HEWLETT:

A. Yes, with the exception of DNA and INA, but regular sort of proteins like -

COFFEY, Q.C.:

Q. IHC sort of stuff.

MR. HEWLETT:

A. IHC type of proteins.

COFFEY, Q.C.:

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Q. You don't want alcohol participating in the fixation process.
MR. HEWLETT:
A. No. Because no amount of antigen retrieval can retrieve what is lost.
COFFEY, Q.C.:
Q. What's completely gone. And as well, it can result in up to the loss of about 40 percent of the protein as well.
MR. HEWLETT:
A. Exactly.
COFFEY, Q.C.:
Q. And we've heard, in fact and I'll take you through this, we've heard Dr. Dabb speak a little bit on that in terms of just, not in the same detail you have, but he has alluded to that here from the Commissioner, the idea of the potential negative consequences of alcohol getting involved -
MR. HEWLETT:
A. It's essential, I believe for you to understand these things if you're trying to get a grasp of, you know, what's going on in an immuno lab. I won't bother you with the morphology, but these are two pieces of the

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same tissue, one on the left is formalin fixed; the one on the right is alcohol fixed and even without being aware of histological structures, you can see significant differences. So there are morphological differences and tinctorial differences and basically look at the shrinkage of the nuclei, the blue structures, tiny blue structures on the right, compared to the left. And the holes between cells, the clear areas on the right, compared to the right, there are many more, well that's protein that's been lost. So I'm going to skip these, but very briefly formaldehyde fixation has the most realistic life like morphology and offers the widest range of histochemistry. There were demonstrations we may wish to perform, including immunohistochemistry. On the other hand, alcohol is great for nuclear morphology, which is why cytologists like it. It's great for the staining of nuclear proteins, RNA and DNA but it greatly restricts the range of histochemistry. So that's the first reality. The widest range of histochemical stains and I think that is a clue to why formaldehyde is

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such an important fixture for clinical specimens. We often do not know what we require--we are required to do up front until after we fix the tissue, it depends on the pathology and so having, you know, freedom to, as it were, to go where we wish, is very useful and all of this was looked at years ago and modern technology steps into place and I recall as a student hand processing tissue through the steps that you've seen described. And then in the 50's, automated tissue processors were introduced and this is one of the earlier ones and you can see it's just a mechanical device which basically carries a basketful of cassettes, dunks them up and down in a solution and picks them up in the air and transfers them to the next one. We thought we died and gone to heaven. Prior to this, our process took up to five days and we'd have to pick a spot where we could leave the tissue safely while we went home to sleep and come back the next day to continue the process. This allowed us to perform this overnight while we were asleep, it was great. And morphologically there was really no difference

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between hand processed and machine processed, providing the material was properly fixed. And so that's the second reality, there is no loss of morphology due to the inherent nature of an automated processor. But, of course, humans being what they are, progress is made and modern fancier equipment comes along and so in the late 80's the closed processes started to come in, electronically controlled with flexible timers and pressure and heat controls and all sorts of things. And again, it's just a wonderful thing. Except people started to abuse the technology with inappropriate use of the technology and the end result was that if we look at on the left an automated formaldehyde fixed processed piece of tissue, compared with what comes out of today's modern processor, again, you'll see these tinctorial and structural differences because it was decided that if automated processing is such a good thing, why don't we put the fixative on there as well and automate the fixation. And turn-around time became king and, you know, the whole thing now happened overnight, forget proper fixation.

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Fixation was on the machine, therefore we can just put the tissue on the machine. There's reality number three. There was a change in morphology, but pathologists and histologists just accepted this, it was acceptable and it became routine and in fact, many pathologists trained post automated processing probably wouldn't even recognize correct fixation because they had never seen it in most instances. There are no standards, and I'm sure you've discovered that already. Those standards that do exist are usually of a local subjective nature such as, you know, we've always done it this way, it looks okay or my pathologist likes us to do it this way. Those are hardly standards. And it's important to understand that variation in one technique may or may not cause sort of a cascade effect, and so people will think, well, I've got this problem, I think the cause is this, so I'm going to change this, whereas the real root cause of the problem, if it's real, may be something completely different, but they've now changed the process. That was done empirically and then the glad tidings were

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often spread by mouth, and other people thought, oh, that seems like a good idea, I'll do it too, and that was the beginning of the end, you know, and things got wildly out of hand. A very brief example, this is a gastric biopsy which is routinely fixed and processed overnight, the technologist reported that it felt gritty on sectioning, and if we look at a higher power, you can see there is obviously some sort of artifact there, in fact, it looks like venetian blinds, okay. The assertion is made, well, this tissue is over fixed, or over dehydrated, or over processed, and the proposed change would be to change all the processing times to accommodate that. The reality is that the section was being cut too rapidly for its hardness. It was actually under fixed, and hence alcohol fixed, which makes it was harder to cut, and the tech was cutting at the same speed, which gave it the venetian blinding effect. You slow down the speed of cut, the venetian blinding goes away, and no more problems without changing anything other than the speed of the cut. And you'd be amazed how many people have fallen into this

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particular trap. That's the same section, the same block, there's no trickery involved here, just the speed of cutting. And multiply that by all the things that happen in a histology lab. So - is it okay if I start with fixation?

COFFEY, Q.C.:

Q. Actually, if we could, perhaps we'll take the afternoon break and come back and speak to fixatives, fixation.

THE COMMISSIONER:

Q. Yes.

(BREAK)

THE COMMISSIONER:

Q. Please be seated. Mr. Coffey.

COFFEY, Q.C.:

Q. Mr. Hewlett.

MR. HEWLETT:

A. Thank you. There are some myths associated with fixation, and I'm not sure what you've heard, Commissioner, but one of the common ones that's bandied about is that formaldehyde with formalin fixed is at the rate of approximately a millimetre an hour. That is completely wrong. If that were true, then a

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slice of tissue five millimetres thick would take five hours, and a thin needle biopsy, one and a half millimetres thick, would take one and a half hours, and there are people who operate on that basis. The reality is--I'm not going to take you through all of this, but there is a formula where one can calculate penetration, and most people who talk like this about formalin are really talking about penetration rate. There is a formula that can be applied. K is a constant, called a medawar constant, which varies with the fixative. The question really is what is "K". The most likely answer is that the baker approximately 3.6, and we know from the latest data that it must be at least two, which means that the millimetre an hour simply doesn't exist. Essentially, if we take a spherical piece of tissue and drop it into an appropriate amount of fixative and leave it for an hour, 3.6 millimetres from the surface will be penetrated, the centre will be raw, and if we have a little tiny piece, it'll be fully penetrated in that time. There are some numbers based upon a "K" of 3.6. And you can

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see that the penetration time is highly variable. It actually starts out at somewhere around 300 millimetres an hour, and by the time we get down to 16 hours, it's approximately a millimetre an hour, and then as we go longer, it slows more and more. It's proportional to the square root of time. So if we want to double the depth of penetration, we have to go four times as long. That's a very important concept. It follows from that argument that small pieces of tissue will fix faster than larger pieces, or does it; well, not necessarily, because fixation is completely different from penetration. So we've actually penetrated these representative slices and cores, the actual time is 30 minutes to penetrate a five millimetre slice and remember it penetrates on both sides, and the core biopsy in less than five minutes, but there is a paradox, and we've known about this for 70 years. Formaldehyde is one of the fastest fixatives to penetrate tissues, but one of the slowest to actually fix them. The paradox was explained in 1982, and many people remain completely unaware of it. There is a

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chemical reaction which occurs. Formaldehyde binds to the reactive side chains on those peptoids that we looked at on the proteins, and it binds at random, it's completely random. It binds quite quickly, but it's completely random as to which side chain it attaches to, and it forms an unstable addition complex. Once we have a sufficient number of these complexes, and if they are close enough together, they may slowly cross link with each other to form a more stable situation, and this progressive formation of cross links converts the protein to a gel form. And that confers stability on the tissue, but these reactions are readily reversible. How long does this take? Well, in aqueous solutions, formaldehyde which is a gas, becomes hydrated and exits essentially as methylene glycol. Less than one part in 100,000 exists as a free formaldehyde, and it's only the free formaldehyde that can bind to the protein. So the methylene glycol solution penetrates the tissue rapidly, it kills cells, it poisons some enzymes and acts as a preservative, but it's not a fixative. The binding of that tiny

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amount of free aldehyde means that there is no longer any free aldehyde available. It binds very quickly, and over hours the solution decomposes to form more free aldehyde which binds, it starts the clock reaction again, more forms, more binds, and this keeps going on. While this is happening, the protein is undergoing dynamic shifting, changing in conformation, just slightly and that exposes more reactive side chains which combined more formaldehyde and so on. This all takes time. How long does it take? Well, the first real studies were done by Fox and his group in 1985, and he used carbon 14 radio labelled formalin and discovered that it took 24 hours to bind, and to reach a threshold of maximal binding. And that experiment was repeated nine years later by Helander, and he decided it took 25 hours instead of the 24, but the correlation between those times is quite remarkable, nine years apart and with two different kinds of tissues, and it's even more remarkable when you look at what they were using. Fox was using essentially a one cell layer thick slice of tissue, got 24 hours with

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a chemical reaction. Helander is using a four millimetre cube. That is a huge amount of tissue in comparison, and it took 25 hours. So for initial stabilization and fixation to occur, it's the binding time that's crucial and not the penetration time, okay. The reaction rate is the penetration time, plus the binding time. So if we look at our two examples, the thick slice will be fixed - penetrated and fixed in 24 and a half hours, and the core needle biopsy in 24.1 hours. So do small pieces fix faster than large pieces; well, yes, but not by much. It gets even more complicated if we go to thicker. If we double the thickness of Helander's test, and he did this sometime later, it now takes 50 hours for the formaldehyde chemical reaction to finalize, okay, and this is of practical importance if you're breadloafing a breast, obviously you can't cut it one cell ware thick, but five millimetres is a reasonable and attainable thickness. That means the slice is penetrated in 30 minutes, well within the guidelines of one hour, and fixation is commencing but takes 24 hours. The one

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millimetre breadloaf slice -
COFFEY, Q.C.:
Q. One millimetre or centimetre?
MR. HEWLETT:
A. Sorry, one centimetre slice, thank you, will be penetrated in under four hours, but takes 50 hours for the chemical reaction to occur. That's significant in terms of handling large masses of tissue. So the general rule is not greater than one centimetre. And the other method is the optimal fixation time in 24 hours. Now that is the minimal time. Fixation is not completed 24 hours. It continues over time and thought to take at least seven days for final crosslinking, where these cross links are much more stable and permanent. But fixation to 24 hours is sufficient to allow reproducible results.
COFFEY, Q.C.:
Q. Reproducible in -
MR. HEWLETT:
A. In all terms. Immunohistochemistry, regular stains, stabilization of the tissue for processing, etcetera, etcetera, and that is the way it is and one cannot change the

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physical rules of chemistry, and to say that it looks properly fixed, well, acceptable morphology on a routine stain doesn't correlate. It simply doesn't correlate with all the staining methods and that's especially true of immunohistochemistry. So if people say to you, this particular breast section looks under fixed, they can tell that. There are certain criteria. You can say yes, it's not properly fixed. But the real insidious stuff comes after about eight to ten hours where it looks okay, but it's still not properly fixed because of the random nature of this crosslinking and I think that perhaps Bill -
COFFEY, Q.C.:
Q. I think you have an analogy, Mr. Parks, to help the Commissioner understand.
MR. PARKS:
A. Yes. I've been asked many times to explain fixation to people and I liken it to building a bridge and if you took all the steel and put it into place with no bolts or anything in it, that would be your protein as it is today in your body, and the fixation process would be

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the sticking of like 100 bolts into this bridge to complete it, and you know it's going to take 24 hours to put all these 100 bolts in. And what you do is, because it is a random event, you would just hang your construction worker on a rope over it and whatever hole he came closest to is where he would put the bolt first. Then he'd have to come back and get another bolt to go back in, and this is the time reaction. It takes time for each bond to happen. You have to sort of reload and that's what happens where you have to recreate another molecule of formaldehyde. The guy has to come back off of the structure, be given a new bolt and then swung back out and wherever he ends up is randomly where he's going to put this bolt, and this would be going on, and if after, let's say, four hours, you stopped and let's say a storm hit, the same thing as putting alcohol, which is the next step in fixation. If you consider a storm versus alcohol. If a storm hit, you would not know how this bridge would collapse with 25 of the bolts in place. It could collapse to the left. It could collapse to

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the right. It could collapse in on itself, but you'd -
COFFEY, Q.C.:
Q. And it might not collapse at all.
MR. PARKS:
A. It may not, but what you don't know is you don't have any predictability of which way it's going to go. Therefore, every step after that, no matter what you do, because if it collapsed to the left, what you may have done if it collapsed to the centre would be different, but you can't standardize because you don't exactly know what happened, and this is the problem with fixation. If you stop fixation at four hours, which is what a lot of the people going for rapid turnaround times are doing, you are collapsing the molecule on itself or causing distortion from the alcohol, but you have no idea of what has actually happened because of the randomness of the placement of your bolts.

So one day, all the bolts may be at one end. Next day, they may be at the other end. So you cannot predict what will happen and that's what effects everything from that point

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forward, because as you try to standardize your methodology, you want everything to be the same each time you go to do it. So that the next step, you do the exact same thing each time. So if you stop fixation before you've got all 100 bolts in place, you do not know what the next step is going to create. It may work. You may be able to say "well, I'm seeing good results here." But you don't know why you're seeing the good result, and you may have good results today and tomorrow and the next week, and all of a sudden, you have two cases that are negative, and you say "well, they're negative, because I've had good results," but that's--there's no guarantee, because you haven't taken it to a point that you can standardize from that point forward.

So the bridge analogy is you're throwing bolts randomly into this. You have no guarantee of what way it's going to react in the storm, and the same thing with fixation. If you cut fixation short, you have no idea what is going to happen when the alcohol hits it. If you go to the 24 hours and you standardize to that, you've got 95 percent of

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your bolts in place. You've got a pretty standard reaction to the wind. It may shift to the right if the wind is coming from the right. You're going to get a very standard result and then you can do whatever you want afterwards, and that is basically fixation. If you stop it too soon, everything has been so random that you cannot standardize from that step forward accurately.

COFFEY, Q.C.:

Q. Because it will be random the next time?

MR. PARKS:

A. It's random, and that's the whole thing. As soon as you have one random event in the practice of pathology, of the histology, the chemistry of it, every other event is unpredictable.

COFFEY, Q.C.:

Q. I take it then that the idea of utilizing 24 or more hours is, is that this randomness process that's going on, it's gone on long enough that it kind of fills all of -

MR. PARKS:

A. All the holes have -

MR. HEWLETT:

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A. 95 percent of the bolts are in place.

MR. PARKS:

A. So no longer is it that random, because 95 leaves only five little random events, whereas only 25 gives you far more variables and that's what's happening.

MR. HEWLETT:

A. This is where people have some misunderstanding with immunohistochemistry and where even some of the guidelines are wrong where in they may say six to eight hours minimum, and they may well be able to demonstrate ER or HER2, not likely HER2, but ER certainly. There is a paper out there by Neil Goldstein suggesting that the minimum time for reliable ER results is six to eight hours. But if you read his paper carefully, you will discover that he actually fixed eight to ten hours, because he forgot to add in the bit on the processing machine at a higher temperature, which speeds up the bolting action a little bit, not much. So if we were to heat formalin to 37 instead of taking 24 hours to get 95 percent of the bolts in place, it would only take 18 hours.

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COFFEY, Q.C.:

Q. Okay.

MR. HEWLETT:

A. That's well documented. It's tempting to think I'll go to warmer, but no, one does not want to exceed 40 Celsius because also a thermastic (phonetic) heat effect takes place. And so they'll say, well, I'm getting results at eight hours, but then what's your positivity rate? And you may find that on the low end of an acceptable range or even below the acceptable range. Yes, they can demonstrate estrogen receptors, but how consistently and how do you believe a negative when you get one? Because the effect of alcohol fixation is largely to create negative results.

COFFEY, Q.C.:

Q. False negative results?

MR. HEWLETT:

A. False negative results. There are many different protocols in use for immunohistochemistry. Histologists traditionally have been a bunch of entrepreneurs and sort of do whatever they

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like, and so there are all sorts of different protocols for immuno in place, and Clive Taylor suggested there are as many protocols in use as there are laboratories using them. But sensitivity and specificity in immuno varies with tiny, tiny changes in protocol and that results in a wide range of reported results. We need--it's become particularly important today, because of the prognostic and predictive markers which are used to determine patient treatment that if you're just trying to say "does this cell contain cytokeratin?" that may or may not be terribly important to a diagnostic. But these are different. We're saying "ah, this cell expresses estrogen receptors. This patient should respond to treatment."

And so this demands a reliable and reproducible result from an immuno laboratory. This is going to increase as a result of proteomic studies. We are producing more and more targeted therapeutic reagents. They will--many of them undoubtedly require immunohistochemistry to determine entrance into the therapy. And yes, we've got

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standardized kits that we can purchase. We have automated immunostaining instruments. But still the variability of results, both within a lab and between laboratories, is a problem. It's a recognized problem for many, many years.

So many laboratories use quality control, QC, and also supposedly quality assessment or quality assurance activities with various individual steps involved. But unfortunately in many places little attempt is given to the overall integration of these daily activities to assess the total quality. So what do we mean by quality control? QC activities are prospective. In other words, they look forward at what will happen if all the steps in a procedure are followed. It defines a product quality and then perhaps the credibility needed for its purpose.

QC activities are the result of advanced planning and are applied to everything that contributes to the final product, and often we refer to these as online controls. You've heard about external controls. That's an online control.

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Quality assessment or quality assurance, these activities are retrospective. They look back at what has happened with a view to measuring the degree to which the desired outcome was successful, okay. This provides opportunities to modify the processes contributing to the product. These are offline controls. And total quality is a much more holistic look at things. We look at all the steps in all the various processes used and integrate those findings to understand how changes to any of these processes will effect the final outcome, and that may mean we have to experiment to provide providence for any proposed modification of the process.

Just about everyone performs QC of the immunohistochemistry procedure. That is completely insufficient, okay. QA and particularly external QA helps to provide additional information, and as an example, I'll show you two immunostains. The two on the left are stains for cytokeratin. Two on the right are for vimentin. These stains were out of a survey that we ran around, an EQA survey we ran around Ontario and asked them to

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stain the cytokeratin. Everybody has the same target here. These are adjacent sections of the same material fixed in a standard manner, and you can see some labs are successful. Some labs are not.

If we take the vimentin stain, and we provide scores for the quality of those stains, this is the distribution around the province. This is one of our very early surveys. They wouldn't look like this any more. They're all squish together now. But you can see that there's a wide range of results, and that's on a known target. Imagine what the spread would be when the target is unknown? An unknown means you have no idea how it was fixed and processed.

So we need to take a total quality approach and, okay, IHC relies upon a steric interaction, the best fit between an antibodies paratope, that's the little bit on an antibody that recognizes the antigen, and its matching epitope on the target. This is a conformation. It's a three-dimensional structure that fits like a lock into a key. Recognition critically depends on the epitope,

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the antigen remaining unaltered, and yet that's actually what the antibody sort of looks like on a computer graphic. Up at the top where it says FAB, those are the variable regions, the regions which actually recognize the different epitopes and if we take one end of those and combine it to its antigen, the green is the antigen. You can see that in certain spaces, they're interlocking and that's the recognition factor.

So you can imagine that if you damage, on the green molecule, some of those surface structures, the antibody will no longer bind. And it can be antibody dependent. So let's say we have an antibody against estrogen receptor. We'll call it clone 1D5. It recognizes certain structures on its antigen, and we have another antibody, clone 6F11, which recognizes slightly different structures on that surface. They're both the same protein, both estrogen receptor, but each antibody recognizes a slightly different set of structures, and we then improperly fix this. We have no idea which structures are going to be damaged. It could be restricted

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to those structures that 6F11 recognizes, in which case, with that antibody, we'll have a negative stain. Or it could be the 1D5 structures, in which case, with that antibody, we'll have a negative stain. But the other one will work. Or it could be both structures where neither will work, and this is always a concern. We have no idea which structures got damaged.

If we look at immunohistochemistry very briefly, the importance of fixation and processing is that it affects everything else that happens afterwards. To the point of obtaining a section, there are documents out there, Williams is the author of one, saying there are at least 76 variables involved in the process of obtaining the specimen to the point where you get a section, and that's before you start staining. When you get into immunohistochemistry, there are probably a couple hundred more. This is high complexity testing. You cannot ignore any of those variables. Fixation and processing has an impact on just about everything else in immunohistochemistry, including antigen

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retrieval or the pretreatment. You wish me to go on?

COFFEY, Q.C.:

Q. Keep going.

MR. HEWLETT:

A. Okay. So the impact is enormous, and in fact, 90 percent of immuno problems are due to fixation in one way or another. So we have to ask ourselves is our routine histological section really formalin fixed, okay. So whose routine? Yours or mine? There is no such thing.

These are two portions of the same sample. It's a bowel polyp. We split the sample. One portion was processed--fixed and processed by routine A. The other one by a routine B. And again, without going into great amount of detail, on the left, you'll see lots of cleavage, empty spaces, clefts between the cells which are due to shrinkage, a cross appearance to the blue nuclei, and a tinctorial difference compared to the ones on the right. If we then take a similar twin specimen and stain for estrogen receptor, routine A will give us the result on the left.

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Routine B fixation and processing gives us the result on the right, and remember, these are the same patient materials. If you're a one percenter, you'd probably call the one on the left. If you're a ten percenter, you wouldn't. That would be classed as negative. The reality is the one on the right.

HER2, probably heard about HER2, look at what happened with routine A. HER2 is a surface membrane protein. It should look like chicken wire. The section on the right shows the appropriate reaction. Okay, the reddish staining around all the cells, the malignant cells. It looks like chicken wire. That red staining on the left is, in fact, the HER2 protein, but you cannot call that positive. There's nothing surrounding each cell. A positive result must be complete circumferential staining around each cell, more than a certain percentage of them. That is the HER2 protein, but it's completely in the wrong location, and that's due to fixation and processing. So you'd call the one on the right positive, it's a three plus positive. The one on the left, you would ignore and call

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it the negative.

CD117 is another similar surface protein, and again, there are dramatic differences in the results between two different fixation and protein processing schedules.

Perhaps you'll get a little more enlightenment if we look down the electron microscope at samples such as this. More detail is apparent. On the right, you'll see that the cells, nuclei, these sort of oval pale areas like this, the cells are stuck together like a jigsaw puzzle very, very tightly. There's no space in between them. Look at the cells on the left, okay. They are literally torn apart. Now if you were looking for HER2 protein on the surface of those cells, I wonder where it would have gone. Well, you just saw where it went on the previous section. And I'm sorry, the difference here is no difference in the tissue process, same machine, same reagents. But look at the fixation time in formalin. A, on the left, is six hours. Remember, this is the minimum recommended time for some guidelines, and B is the same tissue after 24 hours.

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Why does it happen? Well, if you recall I said that the crosslinking with formaldehyde is reversible, it is. Shorter than 24 hours, fewer crosslinks, rather apart. They are more readily reversible and they are reversed by the alcohol on the tissue processing machine. But alcohol is a fixative. It reverses the formaldehyde binding and then refixes the tissue with alcohol with all the appropriate effects. The shorter the time in formalin, the more like alcohol fixation you will get. There's a list of the results.

And some antibodies don't mind alcohol. There's an antibody structure called chromogranin which actually loves it, whereas the alcohol picks one on the left is showing no staining in this structure here, which is the same as this structure here. Okay, with that particular antibody, it won't work after alcohol. The same is true with this antibody called CEA. That's what it should look like. That's what you get if you put it in alcohol.

ER, these are cultured cells with known reactions to ER. Cells on the left are negative. Cells on the right show appropriate

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staining. That's true of tissue, as well, not just experimental cell cultures.

HER2. What about partial fixation? This is the same cells in fibrin clot after four hours of fixation. The edge of the clot is down here on the left, and you can see it about two to four cell depths in. We have this red staining surrounding the cell, that's HER2 protein. In the centre of the clot, we've got nothing, and in this cell here, you can actually see the protein being stripped off the surface, like pulling a glove off your hand. That's after four hours in formalin. Here's a real world tissue. It's a lymph node stained for HER2 with malignant cells in it. Out near the edge, which is partially fixed after eight hours, we see staining. In the centre here or to the left, there is no staining. This is the transition zone. So this you would call positive. This you would call negative. Which portion of the tissue would you select in grossing? There's no way of knowing at the time of grossing.

As an example, we were a reference lab for HER2. We had a policy in house that all

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tissue is fixed for 24 hours minimum, no excuses. Our positivity rate for HER2 is 22 percent. That is well within the 18 to 25 recommended. When we accepted referred in material as a reference lab, our overall positivity rate dropped to 13 percent. So we split out those tissues that were referred to us from our own. Our rate was 22 percent. The referred in positivity rate was eight percent. That is a significant difference. Also the number of equivocals jumped dramatically. We had a five percent equivocal rate. It went to a 20 percent. That's all because of fixation and processing. The same sort of thing can happen with ER/PR. I'm -

COFFEY, Q.C.:

Q. If I could go back to slide 93, please?

MR. HEWLETT:

A. 93?

COFFEY, Q.C.:

Q. Yes, go back.

MR. HEWLETT:

A. Sorry.

COFFEY, Q.C.:

Q. This formalin--you've titled here a myth,

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formalin fixation for more than 24 hours is over fixation and will destroy immuno reactivity, and reality, number nine, you've noted "there is no such thing as over fixation in formalin. Progressive crosslinking does occur over time. This may lead to masking of antigens. This does not occur within any reasonable time frame, five to seven days, for the majority of antigens of clinical interest." I take it -

MR. HEWLETT:

A. I've tested over 300 antibodies and I don't recall one that it affected actually.

COFFEY, Q.C.:

Q. Okay.

MR. HEWLETT:

A. This is in the literature as well. It's in the references with the handout I gave you. Alba is the author, Effect of Lengthy Fixation on Breast Markers.

COFFEY, Q.C.:

Q. And -

MR. HEWLETT:

A. We have actually tested out to 90 days and for some antibodies out to a year of fixation with

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no problems.

COFFEY, Q.C.:

Q. So here, if we could go then to the next slide, actually slide number 97.

MR. HEWLETT:

A. What we need to do to improve?

COFFEY, Q.C.:

Q. Yes.

MR. HEWLETT:

A. Standardized fixation, it's the key to everything. You can optimize your immunohistochemistry method. There's more than one way of performing these methods. Each one needs to be optimized for the target antigen. So that can be optimized. But unless your target, the tissue itself, has been more or less standardized, there's probably no such thing as a true standardization because of variations in biological activity inherent in all of us, and we can't control what the surgeon does in terms of when he cuts off the blood supply and things like that, but from that moment on, we can standardize. Acceptance of the raw specimen fixation and so on, that we can

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standardize, and if we do that, optimizing immunohistochemistry is a relative snap. I mean, it's really easy. A chimpanzee could probably do it. Not true, if we don't. Then it becomes wildly complex.

COFFEY, Q.C.:

Q. Here you have, under strategies for this is standardized fixation by, and you've got "one, cut thin, three to four millimetres blocks. Two, use a 20 to one fixative tissue ratio. Three, adopt a routine minimum 24-hour fixation time, or, four, fix only special tissue/blocks for 24 hours, or, five, stay with variable routine fixation and hope," and five, I take it, is not a -

MR. HEWLETT:

A. Yeah, take a wild guess.

COFFEY, Q.C.:

Q. So I take it then, Mr. Hewlett, that it would be your view that certainly one would be the first approach, one, two, three, would be the better approach?

MR. HEWLETT:

A. Absolutely.

COFFEY, Q.C.:

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Q. For pathology -

MR. HEWLETT:

A. But there are some exceptions. For instance, I was associated with the pediatric hospital. Pediatric tumours need--the patients need to get on treatment really quickly. There are protocols for that. And so the answer there is providing the material is large enough, split it, rush a piece through just to get the diagnosis. Hold a piece back and fix it properly for all the immuno you're going to have to do on it, or do a quick section.

COFFEY, Q.C.:

Q. Now Mr. Hewlett, in terms of then, if I could, bring up P-3358, please? This is an exhibit that you provided to the Commission and it's entitled "Handout for the NSH," would be the -

MR. HEWLETT:

A. That was last September, yes.

COFFEY, Q.C.:

Q. The September '08 National -

MR. HEWLETT:

A. '08, yes.

COFFEY, Q.C.:

Q. - Society of Histologists, one day

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immunohistochemistry forum. Tuesday, September 16th, 2008. Routine tissue preparation and IHC, fixation/processing revisited. This is an abstract and in fact, the -

MR. HEWLETT:

A. It's actually part of the handout.

COFFEY, Q.C.:

Q. Yes. That was given out at that, and this, I take it, is directed, in itself, at a technical, technically savvy audience. The technologists would be -

MR. HEWLETT:

A. Well, sort of, yeah. Not necessarily completely.

COFFEY, Q.C.:

Q. And but here, in effect, and when I looked at this, in essence, although this detail gets into it a little bit more in terms of the formulas and the numbers, in essence, you've actually canvassed the subject matter of this this afternoon with the Commissioner, haven't you?

MR. HEWLETT:

A. Yes. So that you've have the complete detail

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and you could refer back to it, there's a copy of that.

COFFEY, Q.C.:

Q. And if we could, please, I wanted to ask you a couple of other questions. If you could bring up, please, Exhibit, I believe it's P-0051? This is a QMPLS on-site consultation report done by QMPLS for Eastern Health. It's dated December 7th, 2007, the date and time of the on-site consultation itself. The report, I'll bring you to page six, the actual report itself is dated January 2008. And here, the team leader is Dr. Gregory Flynn, who works, I take it, as the managing director with QMPLS, and you know him well?

MR. HEWLETT:

A. Correct, yes.

COFFEY, Q.C.:

Q. And the consultants are listed here, yourself and a Ms. Laurie Mason.

MR. HEWLETT:

A. Okay.

COFFEY, Q.C.:

Q. So I take it, you did participate, Mr. Hewlett, in the on-site consultation report in

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December of '07?

MR. HEWLETT:

A. Yes, I did.

COFFEY, Q.C.:

Q. And this report was prepared. I'm not going to take you through the actual findings in that itself. I just wanted to, here, under Appendix A, attached at the time, there was-- you had Appendix A, Penetration and Fixation Rates of Formaldehyde, and this again, I take it, is in summary form at the time.

MR. HEWLETT:

A. That's a synopsis, actually a copy of a short article that was published in Microscopy Today, yes.

COFFEY, Q.C.:

Q. At the time you were here, I just want to look at page six actually. Under summary of consultants findings. You speak about that and here you said, "in conclusion, the IHC lab is producing good results which would be interpretable anywhere. There are improvements that could be made to the selection, use and recording of control material, but these are incremental in

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nature," and you go on to talk about it and within the report itself, there are suggestions and recommendations and so on.

What I wanted to ask you was this, at the time you were here in December of '07, did the process you were involved in then, in reviewing the lab, extend out as far as the one you've just completed now?

MR. HEWLETT:

A. No, it was strictly the immunohistochemistry lab.

COFFEY, Q.C.:

Q. Itself.

MR. HEWLETT:

A. We had a breeze around the laboratory and a quick look see, but there was no detailed inspection of the remainder of the laboratory. We were there to look at the practices of the immunohistochemistry lab.

COFFEY, Q.C.:

Q. One further point I wanted to ask you, Mr. Parks, is this, it's readily apparent here, based upon the evidence the Commissioner has heard, that beginning in 2005, I mean even locally, they did some retesting of blocks

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from 2002 and other--particularly 2002, but other years as well, and using a Ventana XT and had a number of originally negative ER results convert to positive and they went apparently like from negative zero to strongly positive. That's what we were told by Dr. Carter. And as well then, subsequently, there was a large scale retesting between 1997 and 2005, the samples from that time period that was conducted in '05/06 at Mount Sinai. They used a DAKO, I understand, in that particular retesting process, and quite a number of samples converted from negative in the sense of zeros to anywhere from zero to one to zero to 100, in effect.

I ask you, and they're utilizing though the same blocks. Now I appreciate the protocols would have been different here with the DAKO here, autostainer here, and then the DAKO--the Ventana here, and Mount Sinai's DAKO would have--the system up there, would have used a different protocol. But what, from your perspective, might account for--you know, what possible factors, bearing in mind you're utilizing the same blocks, for going from zero

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to 90 or zero to 100?

MR. PARKS:

A. Well, one of the things that was covered in Bryan's thing was the antibody being used. Each antibody has a different epitope that it is looking for or trying to attach to, and I don't know what antibody they were using at Sinai here, but I know just between the DAKO and the Ultra or the Ventana, there would be a different antibody in use. Different antibodies will--the antigen site can be damaged in improperly fixed tissue, which is -

COFFEY, Q.C.:

Q. Okay.

MR. PARKS:

A. - again, we go back to this. It may be whatever clone they were using that may have been an epitope that was far more open to destruction and -

COFFEY, Q.C.:

Q. By inadequate fixation or tissue processing?

MR. PARKS:

A. By inadequate fixation and processing, the whole--that whole front end, if that is not done properly, especially the fixation. If

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the fixation is incomplete, then there's damage to the molecular structure. The epitope you're trying to identify is different with each antibody. If you're using a different antibody, you can use the same block and you can get very, very different results, absolutely. You can have a negative and a strongly positive based on the damage to the epitope due to improper fixation.

COFFEY, Q.C.:

Q. Okay.

THE COMMISSIONER:

Q. Mr. Parks, is the assumption that if they were proper fixation then the results that you could expect from using different antibodies would be, if not the same, at least within a reasonable range?

MR. PARKS:

A. It would be within standard deviation.

THE COMMISSIONER:

Q. Deviation.

MR. PARKS:

A. It would be very much.

MR. HEWLETT:

A. There is published evidence to that actually

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from UK NEQAS, Commissioner.

THE COMMISSIONER:

Q. Okay.

MR. HEWLETT:

A. Where again, like us, they put out the standard fixed product and see how labs perform and all their studies for ER indicate equivalent sensitivities between 1D5, 6F11, SP1.

THE COMMISSIONER:

Q. They may be attaching themselves to something different.

MR. PARKS:

A. But it's always - it's preserved.

THE COMMISSIONER:

Q. But all the bits and pieces are there to attach oneself to?

MR. PARKS:

A. Exactly.

THE COMMISSIONER:

A. And if it's improper fixation, then -

MR. PARKS:

A. The damage, we don't know what was damaged, so it might -

THE COMMISSIONER:

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Q. And it might be the one that responds to one antibody as opposed to one that responds to -
MR. PARKS:
A. Exactly.
THE COMMISSIONER:
Q. Or bits and pieces.
MR. PARKS:
A. Exactly.
THE COMMISSIONER:
Q. If you'll excuse my non-scientific language.
MR. PARKS:
A. That's very accurate.
MR. HEWLETT:
A. Actually, it goes a little further because those antibodies require antigen retrieval, and depending upon what's damaged and not damaged, and what's cross-linked and what isn't cross-linked, which also varies with the degree of fixation, then the time of antigen retrieval used can make a marked difference.
COFFEY, Q.C.:
Q. So it's not just the anti -
MR. HEWLETT:
A. Oh, no, no, no.
THE COMMISSIONER:

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Q. It's a double layer.
MR. HEWLETT:
A. And there's a third layer because those two machines are using two different detection systems with different sensitivities.
MR. PARKS:
A. But to get exactly what you were saying, if they were all fixed properly, then you would expect all your results to be very close for all the different antibodies and that's why right now you can use all these different antibodies in your lab as long as they meet the requirements. Some hospitals are using - in Ontario we have, what, five or six right now, different types of ER/PR - ER being used, and we're all getting similar results.
MR. HEWLETT:
A. But again the target they're being presented is standardized unit -
MR. PARKS:
A. But--yeah.
THE COMMISSIONER:
Q. Okay, thank you.
COFFEY, Q.C.:
Q. If I could, while I'm thinking of it, Mr. Hewlett, you did indicate that you had prepared another presentation, in fact, that you already have that you didn't have with you.

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MR. HEWLETT:
A. I'm sorry?
COFFEY, Q.C.:
Q. You said - you were telling the Commissioner that you had had another presentation - another slide presentation. That, in fact, you had -
MR. HEWLETT:
A. I was putting one together that I would have brought in -
COFFEY, Q.C.:
Q. I take it, it would have been what, dumbed down a bit, or sophisticated up?
MR. HEWLETT:
A. It would have been about the same level, actually.
COFFEY, Q.C.:
Q. The same level, okay.
MR. HEWLETT:
A. And perhaps a few more illustrations. I mean, I still have illustrations here, but not as

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many as I would have used. I got, for instance, illustrations showing the effects of an in-house control that was a system optimized with an in-house control that was incorrectly fixed, and getting a negative result with a standard fixed material. So they optimized on their in-house control, which is their external control. How was that fixed and processed? They're using that as a standard for - I mean, it's a house of cards, right. You don't know what your control really is because you don't know how it was fixed and processed, but you know it stains. So you now use that as a standard to compare the staining of some other tissue, which you also have no idea how it was fixed and processed, and you hope it stains, and if it does, then you assume it's correct, and if it doesn't, you also assume it's correct because the controls are working, but if it's not an internal control that works, then that gives more credence to it, but what happens if you have an internal control that doesn't work. That could be so. Again you have no idea now. So an in-house control, that is an external

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control, has to be a standard control and you have to set up for that.

COFFEY, Q.C.:

Q. And that would be true not only, I take it, for ER and PR stains, but for the whole gamut of -

MR. HEWLETT:

A. Everything. A lot of people misunderstood Dr. Rhodes paper about antigen retrieval where he says it was the most important part of the whole process. It was true from his perspective because he was dealing with the results of sections sent to 200 odd labs, but the sections that were sent for staining were probably fixed and processed to a standard.

COFFEY, Q.C.:

Q. To his knowledge, to the researcher's knowledge, they knew that these were -

MR. HEWLETT:

A. Oh, yes, yes, UK NEQAS slides are prepared that way, as are ours. So you know the target you sent them. Their in-house controls may have worked, but the one you sent them didn't, and the advice from UK NEQAS would be to increase your antigen retrieval and now it

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works, but the lab's argument is our in-house control worked, so everything is fine, but maybe you hadn't fixed and processed your in-house control properly because that is what you standardize to, what you optimize to, and was it a high level control, or a moderate level control, or a low level control. Most labs use high level controls. That's an absolute recipe for disaster.

COFFEY, Q.C.:

Q. You're in favour of the -

MR. HEWLETT:

A. Well, I prefer to see all dynamic range there, but you should have a negative, a low expressor, moderate, if that's all you can get. If I were to drop a control, it would be the high level expressor because it doesn't really tell me much of anything. A piece of normal breast within a normal duct has all the dynamic levels of expression normally.

COFFEY, Q.C.:

Q. Those are the questions I have, Commissioner. Thank you.

THE COMMISSIONER:

Q. Thank you. Mr. Pritchard?

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MR. PRITCHARD:

Q. I don't have any questions.

THE COMMISSIONER:

Q. Mr. Simmons.

MR. SIMMONS:

Q. Thank you, Commissioner.

MR. BRYAN HEWLETT AND MR. WILLIAM PARKS - EXAMINATION BY MR. DAN SIMMONS

MR. SIMMONS:

Q. Good afternoon, gentlemen, and that's the first time I've ever been able to say that when I've been examining anyone in any proceeding, the first time I've had two people looking at me together. I introduced myself earlier, I'm Dan Simmons. I'm the lawyer here for Eastern Health. There is a number of areas I want to ask you about, and I'll try to move as quickly as I can seeing that it's almost 4:30 already. Mr. Hewlett, we know that you have had some longstanding involvement with the Ontario - with the OLA Program, that's the QMPLS, Quality Management Program for Laboratory Services?

MR. HEWLETT:

A. Yes.

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MR. SIMMONS:

Q. And do I understand that you may have been involved pretty well from the outset of that program, have you?

MR. HEWLETT:

A. For histology, yes.

MR. SIMMONS:

Q. Yes.

MR. HEWLETT:

A. I was an advisor to the committee when it was first set up.

MR. SIMMONS:

Q. Yes, and when was that, the histology program set up, how long ago was that?

MR. HEWLETT:

A. We first ran a pilot in 2000, between committee members and laboratories. The first pilot survey went out in 2002.

MR. SIMMONS:

Q. Okay, and Mr. Parks, have you had any involvement in the QMPLS Program?

MR. PARKS:

A. Yes, I've been a member - committee member since 2003.

MR. SIMMONS:

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Q. And have you both been assessors for conducting accreditation reviews of laboratories in Ontario?
MR. HEWLETT:
A. I have not.
MR. PARKS:
A. No, I have not.
MR. SIMMONS:
Q. But you've both been involved, you say, on the committee?
MR. PARKS:
Q. The committee and also -
MR. HEWLETT:
A. And for EQA.
MR. SIMMONS:
Q. And for EQA:
MR. HEWLETT:
A. Yes.
MR. PARKS:
A. That is the assessment of slides sent in from hospitals. We have - Bryan usually organizes them, but I've sat on several of the co-review panels that review all the slides that come into the centre.
MR. SIMMONS:

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Q. Are either of you able to tell me how it came about that QMPLS exists and plays the role that it does in Ontario in relation to histology labs? Why has it come to be?
MR. HEWLETT:
A. Oh, dear, I'm not sure I'm fully aware of the background to this, but as I recall, 30 odd years ago a group of laboratory physicians felt there should be proficiency testing in the laboratories, and they organized a program which I believe was initially called LPTP, it may have had another name right at the beginning, to provide proficiency testing for Ontario's laboratories. This was organized under the auspices of the Ontario Medical Association with funding from the Ministry of Health and long term care, and the initial disciplines were, I believe, biochemistry, and - I think just biochemistry initially, but since then all of the disciplines have been brought in and histology was the last.
MR. SIMMONS:
Q. Okay.
MR. HEWLETT:
A. And that LPTP was strictly a proficiency testing organization.
MR. SIMMONS:
Q. Yes.
MR. HEWLETT:
A. And I can't give you the date because I'm not sure, but at some point it merged into QMPLS as the EQA Division.
MR. SIMMONS:
Q. So the first survey you call it for histology under the QMPLS Program went out in 2002?
MR. HEWLETT:
A. Yes.
MR. SIMMONS:
Q. Prior to that, what kind of review process existed in Ontario in any systemic way to review the quality of the work that was being output by histology labs in the province?
MR. HEWLETT:
A. Only indirectly via lab licensing.
MR. SIMMONS:
Q. Okay.
MR. HEWLETT:
A. So it was on-site inspection by the lab licensing.
MR. SIMMONS:

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Q. And who licenses the labs in Ontario? Is it a provincial program operated by the provincial government?
MR. HEWLETT:
A. It's a provincial program, and - I don't want to mis-speak, but it used to be the Ministry of Health and Long Term Care, I believe, but now it's done under the auspices of OLAP.
MR. SIMMONS:
Q. Okay, which is?
MR. HEWLETT:
A. Ontario Laboratory Accreditation Program of QMPLS.
MR. SIMMONS:
Q. Right, okay. All laboratories in Ontario doing histology work have to be accredited and licensed, do they?
MR. HEWLETT:
A. Yes, as do staff.
MR. SIMMONS:
Q. Now you mentioned the EQA Program. That is an external quality assurance program?
MR. HEWLETT:
A. Yes.
MR. SIMMONS:

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Q. Can you tell me just a little bit of how that program works?
MR. HEWLETT:
A. We - at the moment the model is that we circulate unstained slides to all laboratories, along with a questionnaire as to how they're doing certain procedures, and we ask them to do certain stains. The main module consists of an H & E or their routine, we call it, an oversized stain, plus three additional special stains. That's the routine module that goes out to every lab performing histology. In addition, we have licensing for immunohistochemistry labs. There are fewer of them, currently 50, whereas there are 78 histology labs.
MR. SIMMONS:
Q. So there are 50 laboratories in Ontario performing immunohistochemistry?
MR. HEWLETT:
A. Performing immunohistochemistry, yes.
MR. SIMMONS:
Q. Yes.
MR. HEWLETT:
A. They get a separate survey, which is normally

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four different antibodies.
MR. SIMMONS:
Q. Okay, and so the unstained slides are sent out to the labs?
MR. HEWLETT:
A. Yes.
MR. SIMMONS:
Q. The labs stain the slides?
MR. HEWLETT:
A. Using their regular protocol. They're supposed to treat these as patient specimens.
MR. SIMMONS:
Q. Yes.
MR. HEWLETT:
A. They return the stained slides along with their in-house exterior controls for assessment back to QMPLS.
MR. SIMMONS:
Q. Do they submit their pathologist's interpretation of the results?
MR. HEWLETT:
A. No, they do not.
MR. SIMMONS:
Q. So it's strictly the staining?
MR. HEWLETT:

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A. Yes, we do not assess pathologist's interpretation of these as yet, or if ever.
MR. SIMMONS:
Q. And I presume then the slides are assessed and the results are reported back to the participating laboratories, are they?
MR. HEWLETT:
A. Yes, they are given a score.
MR. SIMMONS:
Q. Pardon me?
MR. HEWLETT:
A. They are given a score.
MR. SIMMONS:
Q. Since this began, and this began in 2002, you say, with the first survey, what observations have you made, if any, about whether there's been variability in the staining among labs, and if there's been any improvement in what you see coming from labs over time?
MR. HEWLETT:
A. Do you mean overall or any specific -
MR. SIMMONS:
Q. Overall.
MR. HEWLETT:
A. Yes, there's been improvement over time,

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sometimes marked improvement, and it seems to be consistent. We also issue what's called a performance history report, so we track a particular stain at least three surveys.
MR. SIMMONS:
Q. Uh-hm.
MR. HEWLETT:
A. And see if it's consistent performance.
MR. SIMMONS:
Q. How significant was the variability that you would see form lab to lab when you first began sending out these surveys for immunohistochemistry labs?
MR. HEWLETT:
A. Oh, it was pretty big, very significant. I mean, from complete failure of stains to absolutely first class results.
MR. SIMMONS:
Q. Okay. Aside from continuing the EQA Program and sending out more surveys, does QMPLS then taken any other steps to try and improve the quality of the work done by those labs, the programs?
MR. HEWLETT:
A. Yes, we put on educational workshops.

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MR. SIMMONS:
Q. Yes.
MR. HEWLETT:
A. We've been all over the province of Ontario with special stains in immuno workshop.
MR. SIMMONS:
Q. Uh-hm.
MR. HEWLETT:
A. And attempting to teach laboratories to interpret their own results in a similar manner -
MR. SIMMONS:
Q. Uh-hm.
MR. HEWLETT:
A. To the way our assessors do.
MR. SIMMONS:
Q. Uh-hm.
MR. HEWLETT:
A. We have - as well as issuing the results to laboratories, we issue a bulletin called "Committee Comments", which is again an educational component which gives broad strokes to the participants as to what happened overall. They are compared to their peers on their own score sheet, but we also on

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Committee Comments talk about trends overall, and, you know, things we have noticed and suggestions for improvement and so on.
MR. SIMMONS:
Q. And accreditation of immunohistochemistry labs and histology labs, I guess generally in Ontario, did that begin about the same time, in 2000 or did that pre-exist?
MR. HEWLETT:
A. Oh, no, they've always been accredited.
MR. SIMMONS:
Q. It's always been there?
MR. HEWLETT:
A. Yes.
MR. SIMMONS:
Q. And presumably for accreditation, there has been - for a long time there have been criteria known to the labs they had to meet and there's been assessments of those labs against those criteria?
MR. HEWLETT:
A. Yes, indeed, yes.
MR. SIMMONS:
Q. Now have you had - have either of you had any experience in other provinces of seeing the

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way labs work or doing assessments of labs in other provinces aside from here in Newfoundland?
MR. PARKS:
A. I don't. I only have Ontario.
MR. HEWLETT:
A. Only superficially in Quebec. I was invited to go and make some presentations. In parts of Manitoba, yes.
MR. SIMMONS:
Q. So I take it then neither of you would be in a position to make any comment on the state of accreditation or licensing or other quality measures in labs elsewhere in the country?
MR. HEWLETT:
A. Other than I am aware that some provinces either currently have it or are pursuing it.
MR. SIMMONS:
Q. Sorry?
MR. HEWLETT:
A. Either currently have it or are pursuing it.
MR. SIMMONS:
Q. Okay. Now another fairly general question for you. You both have considerable experience with immunohistochemistry,

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immunohistochemistry staining over a period of time, and I wonder if either or both of you would be able to make some comment on what you've seen in regards to the development and change progress of immunohistochemical staining since it's first been instituted, how did it start how, how complex has it become, where do you think it's going in the future?
MR. HEWLETT:
A. Maybe both of us can answer it. Do you want me to take it from the early stage?
MR. PARKS:
A. You do the early stages.
MR. HEWLETT:
A. When did you start?
MR. PARKS:
Q. '82.
MR. HEWLETT:
A. Okay. I first was exposed to immunohistochemistry back in the late '50s on a research basis where we used either fluorescent compounds to label the antibodies and hence detect their sites or radioactive compounds labelling antibodies, but the radioactive compounds, these were applied to

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sections and then subsequently in the dark, a film, a photographic film was laid out at the top. You had to keep them in the dark and wait for a while and then develop the film. You could see black dots and lines where radiation had triggered. It's pretty primitive stuff. The fluorescence label ones, in those days we actually had to build our own fluorescence microscope to observe them, and that was intriguing. There were technical challenges, should we say, but it was a very interesting learning experience. Normally we used frozen material, frozen sections, not paraffin material, or even fixed material, but then later on that developed so we could use fixed material, and eventually paraffin sections fixed material. That was a world of freedom because frozen section fluorescent immunohistochemistry is a femoral (phonetic). You can watch it fade while you're observing it under the microscope. So you have to capture pictures very quickly.

MR. SIMMONS:

Q. So by the 80s then the standard, I guess, was using paraffin embedded formalin fixed tissue?

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MR. HEWLETT:

A. Oh, yes, it started actually - we were doing some paraffin immuno fluorescence in the mid 60s, and it was about the same time they introduced the enzyme labelled peroxidase, and then immediately we switched from fluorescence to peroxidase and attempted to get away from the frozen sections and apply these things to paraffin sections, and by mid '70s, it was a very regular process to use formalin fixed paraffin embedded material for the lymphoma markers, immuno globulins, and -

MR. SIMMONS:

Q. Okay.

MR. HEWLETT:

A. - but relatively restricted a number of antibodies.

MR. SIMMONS:

Q. I'll jump--I'll move you up to the end of the 80s, early 90s. How widespread was the use of immunohistochemistry in Canada, and how many antibodies would be available compared, say, to today?

MR. HEWLETT:

A. Oh, I'd say about mid '80s, it was fairly

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widespread.

MR. SIMMONS:

Q. Uh-hm.

MR. HEWLETT:

A. And an average lab would - a high intensity lab might have 50 or 75. By early '90s, that was up to 130 to 200.

MR. SIMMONS:

Q. From that time to today, what kind of progress has there been in the knowledge and understanding of the basics of how IHC works and of the technical side of what needs to be done to successfully do the testing?

MR. PARKS:

A. I think the knowledge was there back in the 70s and 80s, the basics of it. What has happened a lot is a lot of new techniques have been brought out a lot by the companies looking for new ways to amplify the signal, increase sensitivity, these kinds of things, the balance in immuno specificity and sensitivity, and they've found a lot of new methods of trying to do this using different - it used to be the standard path, and ABC which was just antibody - building on antibodies to

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give you an amplification, and now they are using, you know, molecules and stuff and the antibody reaction is only taking place at the beginning. So it has changed a lot, but basically what we're doing is still very much back to what we were in the 80s. We were doing antigen retrieval.

MR. SIMMONS:

Q. Uh-hm.

MR. PARKS:

A. We were using a lot of the same antibodies and the same clonals being used right now that were used in the 80s when I was doing it, and definitely in the 90s.

MR. HEWLETT:

A. There were more of them.

MR. PARKS:

A. Exactly.

MR. HEWLETT:

A. There were more choices. The technology of automated instruments and kits and so on has dramatically changed.

MR. SIMMONS:

Q. Uh-hm.

MR. HEWLETT:

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A. And quite frankly, it has become - in my view, anyway, there has become associated with that sort of the marketing mumbo-jumbo where, you know, if you buy our product, everything will be wonderful. The reality is that unless the people performing these stains have the basic understanding, the world isn't wonderful. In fact -

MR. SIMMONS:

Q. And Ontario, I take it, has addressed that through the QMPLS and licensing and accreditation to ensure that there's been a level of qualification of the people who perform this testing in Ontario. Has there been any similar national initiative that you are aware of until recently to try and ensure that that same level of qualification exists across the country?

MR. HEWLETT:

A. Not that I'm aware of, no.

MR. PARKS:

A. I have not been made aware of any. Most of our stuff is based on Ontario.

MR. HEWLETT:

A. We do have national certification for the

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technologists.

MR. SIMMONS:

Q. Yes.

MR. HEWLETT:

A. We've had that for many, many years.

MR. SIMMONS:

Q. Right, and that's the basic certification that you've told us about, just the basic skills?

MR. HEWLETT:

A. Actually, there's an advanced certification as well. There are very few of them. I think at last count there were 38 of us, and probably at least four of those are retired like myself, but not active.

MR. SIMMONS:

Q. In the reports that you've presented following the reviews in the four authorities here in Newfoundland, in your conclusions when you assessed the overall results, you compared the tissue fixation processing and so on to two standards that you quoted, both related to HER2 testing, the ASCO standard and the new Canadian Consensus Guidelines, and to the Ad Hoc Consensus Guidelines to be published, which are the ones Dr. Dabbs and you, Mr.

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Hewlett, spoke of. Those standards, how - what part of the process beginning with removal of tissue through to the staining do they cover, how much of that?

MR. HEWLETT:

A. They cover everything from the pre-analytic through to reporting.

MR. SIMMONS:

Q. Yes, and the HER2 guidelines from ASCO and the Canadian Consensus, how long have those been available?

MR. HEWLETT:

A. They're - the updated ones -

MR. PARKS:

A. The Canadian one has been a year.

MR. SIMMONS:

Q. One year in Canada?

MR. HEWLETT:

A. There was one prior to that, and then prior to that the original HER2 testing guideline was Ontario only.

MR. SIMMONS:

Q. Yes.

MR. HEWLETT:

A. It was a QMPLS guideline.

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MR. SIMMONS:

Q. Okay. So those are relatively recent initiatives when we look at the history of this testing.

MR. HEWLETT:

A. Yes.

MR. SIMMONS:

Q. Prior to those initiatives, have there been any other similar guidelines to give guidance to labs across the country for the fixation phase, the tissue processing phase of this?

MR. HEWLETT:

A. No, only good science. If you ask any technologist, let along a histo technologist, what is the most important thing, they will 99 percent of them answer it was fixation.

MR. PARKS:

A. But there are no guidelines anywhere. It is up to the people of the hospital.

MR. SIMMONS:

Q. To either have the resources available for their staff to work these things out on their own, or to find someone like yourselves that they can go to for guidance and help, but there has been no national source, no set of

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guidelines put out by anyone to, for example, say 24 hours is the minimum fixation time that is necessary?

MR. PARKS:

A. Absolutely not.

MR. HEWLETT:

A. No.

MR. SIMMONS:

Q. And if we go to the published literature, you will find that there will be authorities in the literature that will say things different than 24 hours as the minimum?

MR. HEWLETT:

A. And some of them recent.

MR. SIMMONS:

Q. And some of them recent, yes. In your view, that would be wrong, but someone without your opportunity to have the expertise and background that you have in it, might not be in the same position to reach those conclusions?

MR. HEWLETT:

A. No, but it doesn't - it doesn't stick to the published scientific literature on this. That is quite straightforward.

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MR. SIMMONS:

Q. Okay. Where do you - where do you think we in Canada should be going in developing some sort of more national approach or standard to the implementation of standardized fixation and tissue processing? How do we get there?

MR. PARKS:

A. How do we get there?

MR. HEWLETT:

A. Well, it's a separate question.

MR. PARKS:

A. It's a very good question.

MR. SIMMONS:

Q. Two questions, yes.

MR. PARKS:

A. The thing with pathology is we are - act as if we're servants to the clinicians and to the surgeons, and we take their needs or their apparent needs of these rapid turnaround times and things like that as our guiding in how we're developing our methodology, which is exactly the opposite the way it should be. Pathologists need to, and pathology people, technologists, need to assert that we can only give you so much information from the specimen

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if you force us to do these rapid testing. Basically, you're saying - my thing is, and it was said kind of jokingly about ten years ago, but it's - I said we should have a stamp that says these results, we can only go to this certain point if you insist that we turn the specimen around in eight hours or so, or only allow eight hours for fixation because your results are not reliable. We need to assert ourselves to the people that we are providing a service to that you're asking for far more from our - you're asking for far more detailed results that you were 25 years ago, and the practice of fixation has not really changed much in those 25 years. So what's happening is 25 years ago you were asked to give a diagnosis whether this tumour was benign or malignant, and they were using that to base their treatment. Now they're asking the pathologist right down to molecular level, how is this going to respond to this drug. They are basing their therapy very heavily on what the pathologists are giving them. Before it used to be, well, this is a benign tumour, this is malignant, we're going to treat it

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this way. Now they want very specific answers because the drugs are only going to react to a person who shows positivity, but they're asking for information that we can't give them if we are not allowed to standardize our fixation, and this is where I feel that we need to, as province, country, whatever, we need to set guidelines, quite honestly.

MR. HEWLETT:

A. The other issue is - I'm sorry to interrupt.

MR. SIMMONS:

Q. No, go ahead.

MR. HEWLETT:

A. The other issue is often from an administrative side, guidelines seem to be set in terms of turnaround time, and it's important I think that people understand in the words of the past chairman of our committee, there is a difference between speed and timeliness, and neither should be allowed to interfere with accuracy of results, and the turnaround time people have basically overridden our science.

MR. SIMMONS:

Q. In the Ontario program, has QMPLS standardized

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fixation and processing in the way that you're promoting in the reports that you've delivered here?

MR. HEWLETT:

A. In every Committee Comments, after every survey we have promoted it.

MR. PARKS:

A. We've promoted it, but it has not ever been -

MR. HEWLETT:

A. We cannot force people to do it.

MR. SIMMONS:

Q. So has - so has it been achieved in Ontario then?

MR. PARKS:

A. No.

MR. HEWLETT:

A. Not totally, but there are a number of laboratories that follow this advice. I think the majority of laboratories now follow it for breast because of the HER2 guidelines.

MR. SIMMONS:

Q. Yes.

MR. HEWLETT:

A. But not necessarily for other samples.

MR. SIMMONS:

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Q. And Mr. Parks, you agree with that?

MR. PARKS:

A. I agree, yes, and there are pockets of it around and there's groups of hospitals interacting with each other which are doing this, but again, there isn't any strong published guidelines that say you must do this, and if we equate--as Bryan said before, blood is a tissue. Chemistry will not do a blood glucose level on a tube that hasn't been treated properly. They won't do it because the results are unreliable. The same thing with hematology. If you give them a tube of blood that has a blood clot in it, they won't do a cell count, and that's what we need to get to, I believe quite strongly, in histology, that we set a standard that will allow us to give you every result you want from that piece of tissue, and it has to be, I believe, in a strong sort of guiding recommendation.

MR. SIMMONS:

Q. Okay. So if it were, for example, made part of the accreditation process, there would be-- it would be easier to achieve the kind of

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standardization that you're promoting?

MR. HEWLETT:

A. Oh, I think so, but usually accreditation processes don't set those particular benchmarks. They use other guidelines and published standards and say you must abide by these.

MR. SIMMONS:

Q. Right.

MR. HEWLETT:

A. But the accreditation people don't actually set the standard.

MR. SIMMONS:

Q. Is there any body or authority in Canada that would be in a position to adopt authoritative guidelines for fixation and processing that would have the effect of achieving a higher degree of standardization in the country?

MR. HEWLETT:

A. No, I don't believe so. I mean, there's a group with the moral responsibility and that is the Canadian Association of Pathologists can lead that, but they cannot mandate. We've got ten provinces and three territories, and you know, they won't be mandated to. Even the

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Feds, I don't think, can.

MR. SIMMONS:

Q. Okay. Some specific questions for you. First I'd like to go to P-0051, please, which is the report, Mr. Hewlett, that you were involved in after your visit here in December of 2007.

MR. HEWLETT:

A. Um-hm.

MR. SIMMONS:

Q. And I believe that particular report was prepared following the invitation of Eastern Health to come here and conduct a review of the immunohistochemistry laboratory?

MR. HEWLETT:

A. Correct.

MR. SIMMONS:

Q. And there were three reviewers then, Dr. Flynn, yourself and Ms. Mason?

MR. HEWLETT:

A. Yes.

MR. SIMMONS:

Q. Maybe you could just briefly tell me what the roles of each of you were on that review?

MR. HEWLETT:

A. The technical aspects were divided between Ms.

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Mason and myself.
MR. SIMMONS:
Q. Yes.
MR. HEWLETT:
A. And Dr. Flynn was sort of coordinating the on-site consultation.
MR. SIMMONS:
Q. And how much time did you spend here on that occasion?
MR. HEWLETT:
A. All day.
MR. SIMMONS:
Q. And you had the opportunity then to see the state of development of policy and procedure for the immunohistochemistry laboratory -
MR. HEWLETT:
A. At that time, yes.
MR. SIMMONS:
Q. - on that particular visit, did you?
MR. HEWLETT:
A. Yes.
MR. SIMMONS:
Q. Yes, okay. I'm just going to--time is moving on, so I'm going to bring you just to page six, the last page, which has the summary of

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the findings there, and in paragraph 14, the first paragraph, section 14, the statement is made there that "the laboratory is functioning at a comparable level to similar labs in Ontario," and I wonder if maybe you could just elaborate a little bit and explain in what way you saw the immunohistochemistry lab being comparable?
MR. HEWLETT:
A. In terms of size, workload, type of staff. They were very similar, for example, to Thunder Bay, and the immuno lab there, which I'm very familiar with.
MR. SIMMONS:
Q. Yes.
MR. HEWLETT:
A. And I would say yes, they're at a comparable level, perhaps not in the complete documentation, but functioning. They were doing all the right things.
MR. SIMMONS:
Q. And of course, the laboratory in Ontario would have been one that had been going through accreditation probably for a couple decades prior to that and would have had the benefit

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of that degree of oversight and external involvement?
MR. HEWLETT:
A. Yes.
MR. SIMMONS:
Q. Yes, okay. The third paragraph there, you've been referred to this already. You said "in conclusion, the IHC laboratory is producing good results which would be interpretable anywhere" and by that, do you mean that the slides being produced -
MR. HEWLETT:
A. Yes.
MR. SIMMONS:
Q. - the stained slides are ones which could be interpretable and used in a clinical setting -
MR. HEWLETT:
A. And the controls.
MR. SIMMONS:
Q. - anywhere in Canada?
MR. HEWLETT:
A. And the controls.
MR. SIMMONS:
Q. And the controls as well.
MR. HEWLETT:

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A. Yes, we have actually looked--it's not just, you know, an opinion plucked out of the air. Both Ms. Mason and--well, I'm not an active assessor, but I do look at every slide coming in, and they have participated in our EQA surveys.
MR. SIMMONS:
Q. Right, so the immunohistochemistry lab here has participated in your external proficiency testing and submitting slides?
MR. HEWLETT:
A. Yes.
MR. SIMMONS:
Q. And you're familiar with the results of that testing, are you?
MR. HEWLETT:
A. Yes.
MR. SIMMONS:
Q. Yes, and what do you know about that? How has the lab done on that testing?
MR. HEWLETT:
A. They did very well.
MR. SIMMONS:
Q. Okay, and shortly after that statement there, it says "the administration should be

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confident that at this time, the IHC laboratory is operating a high quality controlled ER/PR program."

MR. HEWLETT:

A. That's right.

MR. SIMMONS:

Q. So all three assessors were comfortable and confident in making that statement in that report?

MR. HEWLETT:

A. Yes.

MR. SIMMONS:

Q. Okay. Now when you came here on this trip, you were given a different mandate and this time, the review was confined to, I guess, what we'd call the pre-analytical phase of the testing, and I understand you didn't have any written terms of reference to follow, but you were directed to inquire into those particular areas.

MR. HEWLETT:

A. Yes.

MR. SIMMONS:

Q. Okay, and I presume you were given free access to any people or materials or facilities that

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you needed in order to conduct that review?

MR. HEWLETT:

A. Yes.

MR. SIMMONS:

Q. Did you do an exit interview with any of the staff from the lab?

MR. HEWLETT:

A. Not a formal exit interview. We sort of in talking to the manager and some of the technologists along the way -

MR. SIMMONS:

Q. Right.

MR. HEWLETT:

A. - particularly where they would ask something that we felt we could be helpful with, but our mandate was not to act as consultants to them.

MR. SIMMONS:

Q. No, okay. Does that differ from the normal kind of assessment or review that you may have been called upon in the past to do at other hospitals?

MR. PARKS:

A. With mine, it's very different, because I usually assess a hospital for a day or two and then spend an entire day in the lab

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implementing some changes, discussing the importance of the changes I'm implementing and talking with the staff on a head-on, on the bench sort of thing. I work with them for the day and we discuss problems and stuff and so it's quite different.

MR. SIMMONS:

Q. So in this case, those kinds of things come now from your report instead of from your personal interaction with the people in the lab?

MR. PARKS:

A. Yes.

MR. HEWLETT:

A. Yes.

MR. SIMMONS:

Q. Okay. You've both discussed the issue that was discovered with the VIP5 tissue processor and I wanted to ask you something about the effects of that, but first of all, I want to see if I understand some of the very basics of the way this works. There's four different solutions in a processor.

MR. HEWLETT:

A. Sorry, there are more than that. We're

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talking waxes. There are four waxes.

MR. SIMMONS:

Q. Okay. It starts with the formalin?

MR. PARKS:

A. That's correct.

MR. SIMMONS:

Q. And the purpose of that is really to hold the tissue while you're waiting to start the run?

MR. PARKS:

A. Correct.

MR. SIMMONS:

Q. Rather than to actually continue the process of fixation. Then there are alcohols which are meant to dehydrate the tissue, meaning remove water from it?

MR. PARKS:

A. Yes.

MR. SIMMONS:

Q. Xylene or clearing agent which, am I correct, is meant to remove the alcohol?

MR. HEWLETT:

A. Yes, and to render the tissue miscible with the molten wax.

MR. SIMMONS:

Q. Okay, and so it prepares it for the -

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MR. PARKS:
A. Exactly.
MR. SIMMONS:
Q. And then the wax is applied so that when the tissue is embedded, it's fixed in a block and it's physically easy to--possible to handle it and cut it? Is that the very basics?
MR. HEWLETT:
A. The wax is allowed to solidify and so essentially the tissue and the wax block become one.
MR. SIMMONS:
Q. So as far as the preservation of the tissue goes, the wax itself does not play any part in the preservation of the tissue?
MR. PARKS:
A. No.
MR. SIMMONS:
Q. And neither does the xylene?
MR. HEWLETT:
A. Have to qualify that.
MR. SIMMONS:
Q. Okay.
MR. HEWLETT:
A. If the tissue is properly fixed -

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MR. SIMMONS:
Q. Yes.
MR. HEWLETT:
A. - it has little role. It does extract some lipids.
MR. SIMMONS:
Q. Okay, but that's not the primary role?
MR. PARKS:
A. No.
MR. SIMMONS:
Q. Okay. So on this review, you were satisfied, I understand, that the tissues that were going into these processors were appropriately fixed?
MR. PARKS:
A. Yes.
MR. HEWLETT:
A. Everything we saw indicated that.
MR. PARKS:
A. Everything we saw, yes.
MR. SIMMONS:
Q. Yes, and the protocols and policies and procedures that you saw regarding fixation were ones, I think, that you regarded as satisfactory, according to your expectations

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and what you would like to see in place?
MR. PARKS:
A. Yes.
MR. HEWLETT:
A. With one caveat. I would like to see the fixation policy modified and take out that six to eight hour business.
MR. SIMMONS:
Q. Okay.
MR. HEWLETT:
A. But they're only following the Canadian consensus guidelines, but I personally object to that.
MR. SIMMONS:
Q. Okay, good. So the tissue going into these processors then, as far as you are aware, and based on your investigations, was adequately fixed?
MR. PARKS:
A. Yes.
MR. SIMMONS:
Q. So, and then at the end of the process, because of the problem with the processors, the blocks, if I understand correctly, had not had all the xylene removed and there may have

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been some residual xylene?
MR. PARKS:
A. That's correct.
MR. SIMMONS:
Q. Now the effect of that would be, I believe you said, that it would make it more difficult to cut the blocks, because of the physical consistency of the material?
MR. PARKS:
A. Yes.
MR. SIMMONS:
Q. Would there be any other effect?
MR. HEWLETT:
A. Apart from blowing up on the water surface of the section.
MR. SIMMONS:
Q. Which would mean you wouldn't be able to produce an adequate slide and that would be known and obvious to the people making the slides?
MR. HEWLETT:
A. They would be--it's hard to say and this is without real evidence, but as the solvent evaporated from the wax block, the block would cavitate -

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MR. SIMMONS:
Q. Yes.
MR. HEWLETT:
A. And that would tend to put some physical pressures on the tissue itself. I'm not sure what the effect on that would be.
MR. SIMMONS:
Q. Right.
MR. HEWLETT:
A. But there would also be some drying out. If there was sufficient solvent in there, when this evaporated, the tissue is now left dry, so they're hanging partially in wax.
MR. SIMMONS:
Q. Would there be any effect on the antigens necessary to conduct the immunohistochemistry testing later on down the line because of the presence of any excess xylene?
MR. PARKS:
A. If it had dried out significantly, there is a chance there could be.
MR. SIMMONS:
Q. There's a chance there could be?
MR. HEWLETT:
A. Yes.

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MR. PARKS:
A. But like we--the thing it all goes back to is if it's really properly fixed, the amount of damage is limited as we go through. Now there is a chance that with excessive drying that there could be, but it would be hard to detect without doing the scientific work on it to find out exactly what was -
MR. HEWLETT:
A. It's speculation.
MR. PARKS:
A. It is speculation.
MR. SIMMONS:
Q. So at the moment, it's only -
MR. HEWLETT:
A. And I'm not sure if anybody has tried it.
MR. SIMMONS:
Q. Right, okay. So the primary concern then would be the physical condition of the tissue -
MR. PARKS:
A. Exactly, yes.
MR. SIMMONS:
Q. - and the ability to cut a proper section in order to make a slide that you would then send

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to the testing, as opposed to knowing that there would be a problem once the immunohistochemistry testing is done?
MR. HEWLETT:
A. There would--that's right, there would definitely be problems if the tissue were not adequately fixed.
MR. SIMMONS:
Q. Right, okay. And similarly with the comments you made regarding the embedding process and the recommendation to put the wax in the tray, I guess, that the cassettes are held in, if I understand correctly, you're saying that without taking that step, there's a risk that the tissue in the blocks can develop a margin between the tissue and the wax surrounding it and that this can also have some effect on the ability to cut the tissue and make the slides.
MR. HEWLETT:
A. And will be visible in some stains, particularly in immuno stains where the tissue is dried out a little bit.
MR. SIMMONS:
Q. Okay. So, around those edges.
MR. PARKS:

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A. Yes.
MR. HEWLETT:
A. Around the edges.
MR. SIMMONS:
Q. Okay.
MR. HEWLETT:
A. More likely to see something during antigen retrieval as well, you sort of get edge frilling.
MR. SIMMONS:
Q. Aside from the edges though, would the remainder of the tissue be affected in any way in the immunohistochemical staining?
MR. HEWLETT:
A. No.
MR. PARKS:
A. No.
MR. SIMMONS:
Q. It would not.
MR. PARKS:
A. The other issue that I think we alluded to earlier was the fact that if you are dealing with smaller pieces of tissue, there is a danger that when the blade hits that piece of tissue, if it isn't properly bonded, it can

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pop out and be lost. So, that was one of the reasons we brought that up.

MR. SIMMONS:

Q. Okay. You've discussed already the purchased formalin and the pH of it, factual thing. In inquiring about the testing of the pH of the formalin, did you have any occasion to speak to either Mr. Dyer or Mr. Green in the immunohistochemical lab as to whether they knew if the pH had been checked?

MR. PARKS:

A. No, I did not.

MR. SIMMONS:

Q. Okay. I'm taking myself back to Grade 10 science now, is a neutral pH 7?

MR. PARKS:

A. yes.

MR. SIMMONS:

Q. So, when we speak of neutral buffered formalin, are we expecting a pH of around 7?

MR. HEWLETT:

A. At least 7.

MR. SIMMONS:

Q. At least 7, okay.

MR. HEWLETT:

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A. There's a bit of a euphemism in the books. If you do research into buffers and fixation, in most of the serious work talks around physiologic pH which is about of 7.4.

MR. SIMMONS:

Q. Okay. I'm just curious why there would be commercially available formalin with a pH of less than 7 if it's not useful.

MR. HEWLETT:

A. It's interesting, but all the companies out there who produce these things actually commonly make it according to a formula in most standard histological tests which is you follow that precisely, will, in fact, give you a pH of 6.8 to 6.9 because the formula is wrong.

MR. SIMMONS:

Q. And the industry hasn't recognized this and corrected it -

MR. HEWLETT:

A. No, because that's--it's one of those things, we've always done it this way and so that must be right. You know, neutral is sort of--approximately neutral.

MR. SIMMONS:

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Q. How significant would the effect be of using a formalin with a pH of 6.86 rather than one of 7 or 7.2?

MR. HEWLETT:

A. That's hard to say, but we do know that the cross linking will be less. Cross linking increases more towards pH 8 we go -

MR. SIMMONS:

Q. Okay, but the extent--how much less, you're not able to say.

MR. HEWLETT:

A. I don't think it's well documented in the literature. Certainly if you acid it by more than that, there is a known effect on immuno stains, fixing an acidic by formalin is not a good deal.

MR. SIMMONS:

Q. Okay. In the report concerning Eastern Health, you also commented on the program goals, made the recommendation that the one that was listed forth should be the first one. Did you inquiry of anybody as to whether those goals were listed in order of priority or whether they were regarded as having equal priority?

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MR. HEWLETT:

A. No, in all honesty, we did not, but -

MR. SIMMONS:

Q. Or inquire about the providence where the ones you found posted on the wall came from and whether they were a current statement. We did -

MR. PARKS:

A. We did talk to the staff and ask them about the goals on the wall. And they said yeah, that it had been posted and it was -

MR. SIMMONS:

Q. But as far as inquiring as to whether they were prioritized and ranked in order, you didn't make any inquiries of the managers, for example concerning that?

MR. PARKS:

A. We did speak with--on day last there, remember we spoke about it.

MR. HEWLETT:

A. True.

MR. PARKS:

A. We were in this office and we actually said to Barry about that and we were talking to him at that point in time and he seemed to indicate

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yeah, that would -
MR. SIMMONS:
Q. He agreed that the staffing one was one that should now be given an higher -
MR. PARKS:
A. A higher priority, yes.
MR. SIMMONS:
Q. Okay. And regarding the staffing and it's the last thing I'm going to ask you about, I think, regarding the staffing, you made the observation that it would be better if staff weren't moving in and out of positions and if they were progressing through the whole thing, as you observed for the two new people who are being trained -
MR. HEWLETT:
A. Um-hm.
MR. SIMMONS:
Q. - to be the right thing. Did you explore any of the underlying reasons why that may have been the case here and in particular whether there were any labour relations issues associated with that.
MR. HEWLETT:
A. We understood that that was part of -

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MR. PARKS:
A. By speaking to the staff, I spent quite a bit of time speaking to them and asked them why they were moving in and out. And they said because that's the labour, the union and the labour relations -
MR. SIMMONS:
Q. Yes.
MR. HEWLETT:
A. - it wasn't that they weren't happy working there. Actually, they wanted to stay there, but it was the way the union and the hospital operated. And they explained to me that it was a culture, it was an accepted way they had been there for years and that had been going on.
MR. SIMMONS:
Q. And so would it be your understanding that there might, in fact, have to be changes to the collective agreement in order to fully implement the kind of recommendation that you're making?
MR. HEWLETT:
A. I think we were aware of that.
MR. PARKS:

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A. We know that would have to -
MR. HEWLETT:
A. We're talking about an ideal situation and as part of a quality scheme.
MR. SIMMONS:
Q. Okay. Thank you very much, that's all I have for You.
THE COMMISSIONER:
Q. Mr. Browne?
BROWNE, Q.C.:
Q. Thank you, Commissioner.
MR. BRYAN HEWLETT & MR. WILLIAM PARKS, EXAMINATION BY PETER BROWNE, Q.C.
BROWNE, Q.C.:
Q. Good afternoon, gentleman. My name is Peter Browne, I represent a number of the individual physicians who have been asked to testify before the Commission. I just want to go back to--I just have a couple of areas I want to canvas with you and perhaps I'll start with Mr. Hewlett and then Mr. Parks, if you have anything to add.
You had mentioned, I think, in one of your reports related to, I think, Eastern Health report, about the checking of the locks

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by the technician, I guess the end point where the block and the slides are separated.
MR. HEWLETT:
A. Um-hm.
BROWNE, Q.C.:
Q. And I think you emphasized that that is, sort of, the--that's an important departure point because that's, sort of, the end point for the patient in terms of the total quality control of the system within the lab, is that -
MR. HEWLETT:
A. Before delivery to the pathology -
BROWNE, Q.C.:
Q. Correct. And you'd mentioned that, I think one of the labs in Eastern Health, the way this was looked at, the slide looked at was visually and not under a microscope. Did I understand you correctly? Was that--there was a visual inspection of the slide as opposed to the slide being looked at under a -
MR. HEWLETT:
A. That is all it is. It's a visual matching of the stain slide with the block it was cut from.
BROWNE, Q.C.:

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Q. Okay. Is there any advantage to the technician in looking at the slide under the microscope?
MR. HEWLETT:
A. Well, they should be doing that as part of the QC for the H&E stain.
BROWNE, Q.C.:
Q. Right, and that's what I understood at that point, that should that--rather than just visually -
MR. HEWLETT:
A. That--microscopic.
BROWNE, Q.C.:
Q. Right.
MR. HEWLETT:
A. But the final visual check before the slides are released should be a comparison between what's on the stained slide with what's in the block.
BROWNE, Q.C.:
Q. Right. And just so I'm clear on that, that should include looking at the slide under the microscope?
MR. HEWLETT:
A. No.

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BROWNE, Q.C.:
Q. Oh, no?
MR. HEWLETT:
A. You can do microscopic -
BROWNE, Q.C.:
Q. Microscopic--okay, sorry, I wasn't clear on that. Thank you. Now, the next issue and this has come up in a couple of the reports that you have generated for the outside hospitals and perhaps, Registrar, if we could have 3366, page 3. And just--this portion here and then the processing portion down here as well, you mentioned that there was occasional problem with tissue thickness and that these problems were reported back to the pathologist.
MR. HEWLETT:
A. Um-hm.
BROWNE, Q.C.:
Q. And I guess this was noted both in Western where there's a very small number of pathologists and again in Gander, I think as well, as we noted the observation.
MR. HEWLETT:
A. An area that's direct contact.

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BROWNE, Q.C.:
Q. Right. Now, that's a bit more problematic in a larger lab where--and you say, these things do occur, I mean, it's very difficult to get thicknesses. What would be the approach here? Should that be a memo from the lab to all pathologists, sort of, bear this in mind. How would one address that, sort of, problem, if you're noticing this occurring from a number of different, I guess, pathologists throughout the system?
MR. HEWLETT:
A. I don't wish to appear facetious, but my personal approach has always been if it was really bad and affecting my ability to cut the section, it would be to go and get a pathologist and say, can you come over to the microtome here, let me see you cut it.
BROWNE, Q.C.:
Q. But that -
MR. HEWLETT:
A. Then that seems to sink in really well.
BROWNE, Q.C.:
Q. Right, but it's important to get that communication back.

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MR. HEWLETT:
A. Yes, absolutely.
BROWNE, Q.C.:
Q. You were asked by Mr. Coffey to potentially explain, I guess, a change in result, I guess, based on the scenario of the retesting at Mount Sinai. And the hypothetical you were given was a change in--different antibodies used. What if the same antibody was used and cased that, would that change anything?
MR. HEWLETT:
A. Yes.
BROWNE, Q.C.:
Q. What would explain that? Putting aside the answer to the question was fixation, but if the same antibodies were used both here in St. John's, say 6F11 for example.
MR. HEWLETT:
A. Okay.
BROWNE, Q.C.:
Q. Both here and at Mount Sinai, is there any other explanation that may cause that result?
MR. HEWLETT:
A. Yeah, there are three major possibilities. Number one is differences of antigen

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retrieval, not only the heat and time, but also the pH and type buffer used. The second thing would be the actually dilution and incubation time of the antibody. Are they the same or are they different. The third thing would be the sensitivity of the detection system and that ultimately affects the overall sensitivity of the entire test.

BROWNE, Q.C.:

Q. And you'd mentioned, I guess, the association of antigen retrieval on antibodies. And you've indicated, I guess, there's upwards of 300 now in existence. Antigen retrieval use on antibodies, how many of those antibodies with just a, I guess, proportion require antigen retrieval, do most antibodies require antigen retrieval?

MR. HEWLETT:

A. We could say, I think, safely that most laboratories seem to favour using antigen retrieval wherever possible.

BROWNE, Q.C.:

Q. Right.

MR. HEWLETT:

A. Is it necessary? No, not for all of them.

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Each antigen antibody interaction is unique, completely unique. So to have a one size fits all is really not optimum. There are people who do antigen retrieval when it's unnecessary and there are people who don't antigen retrieve when it is. And both seem to get some kind of result with a particular antigen.

BROWNE, Q.C.:

Q. Has that been addressed in any of the standards or direct communication or am I raising a

MR. HEWLETT:

A. You're raising an issue.

MR. PARKS:

A. It's an issue; it's across the country, because unless you're using a closed system such as some of the ones that are out there, they dictate what is going to be done on it, but even then you have the modification of doing different times and stuff. So, it is totally house dependent. Who's house you're in will depend on what is being used. And that is--gets back to the standardization. If you have a standardized bunch of controls, you standardize using that and you're getting

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results, then that's what people are doing and everybody had found different ways to make different antibodies work. And there's some people say, I retrieve 80 percent. There's some places that are retrieving 90 percent. And there are some people down considerably. So, there is no hard set rules.

BROWNE, Q.C.:

Q. Okay.

MR. HEWLETT:

A. As an example, I was at the principle investigators meeting in Florida few years ago for CD117 and I certainly tried antigen retrieval, I stay away from it like the plague with that antibody, but some of the other principle researchers said you absolutely had to antigen retrieve. And when you did that, you got slightly different results. And then it was realized that there was an increase in false positivity when you did that. And the end result of the discussion of supposed experts on this brand new antibody at this time was that, well the best thing to do would be to do two stains. One with retrieval and one without retrieval and see what happens.

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Does that help? The experts don't agree.

BROWNE, Q.C.:

Q. So, you say, it's in a state of flux still?

MR. HEWLETT:

A. Yes.

BROWNE, Q.C.:

Q. Okay. Which leads me to my last question, Mr. Hewlett and again, by all means, Mr. Parks, join in. You're retired. We talked about the importance of teaching and getting this knowledge out and we've heard, the Commission has heard a lot of--any idea about creating a web based classroom?

MR. HEWLETT:

A. I may be retired--I'm so busy. Actually, I am working with the CSMOS and hopefully some of my colleagues to try and put a continuing ed course together, distance education course in immunohistochemistry. I do put on workshops all over the place on a fairly regular basis. So, as it were, I think I'd doing my bit. But there's a limit -

BROWNE, Q.C.:

Q. Sure.

MR. HEWLETT:

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A. - to how far I can take this and besides, you know, maybe it's time for the old fogey to, sort of, fade and let some of the new blood move in with more enthusiasm.

BROWNE, Q.C.:

Q. Well, I think the Commissioner has heard about institutional knowledge and institutional memory and you obviously have a lot of that and it would be important to share that with others. That's all the questions I have. Thank you.

THE COMMISSIONER:

Q. Thank you, Mr. Browne. Mr. Eaton

MR. BRYAN HEWLETT & MR. WILLIAM PARKS, EXAMINATION BY DAVID EATON, Q.C.

EATON, Q.C.:

Q. I'd say good night, but it's not quite there yet. My name is David Eaton, I represent the other health authorities. So, my questions will be primarily for you, Mr. Hewlett, but there are some that perhaps you could each answer.

I'd like to go back, first of all, to the formalin, 10 percent buffered formalin that seems to be used in all of the labs across the

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province. Just if I can summarize what I think you said, which is that this is not a product that is designed for some other purpose. It's a product that just doesn't meet the specifications for the required purpose. Is that -

MR. HEWLETT:

A. Maybe I can explain it best by saying, I looked at the MSDS to find out what the contents were. I expected to see a dual phosphate solvent which is the commonest one. And it's the one that is referred to by most of the guidelines when they say you must fix in phosphate buffers, formaldehyde, it's not-- it's not phosphoric acid in it and sodium hydroxide and that's not a standard buffer. As to its effects, your guess is as good as mine because I've not seen any literature of people testing it. So, we don't know. But if you wish to follow a guideline, then you should follow the correct one which would be a--what everybody accepts to be a phosphate buffered formalin. And that is available from a number of manufacturing. And I have to assume that in this province, there is some

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kind of group purchasing going on because everywhere has exactly the same product and that's a good thing. I just wonder if it was put up to tender and if that was the particular one that was accepted. And that would be a question and my recommendation would be that before putting it out for tender the responsible party should specify this buffer, this pH, there'll be lots of people who can supply it and then go with the best price.

EATON, Q.C.:

Q. Thank you. I have a question about the refrigeration and you made a comment in your report, I think it was the Corner Brook report, I believe it was, about the sample or the tissue going into formalin and then being placed in the refrigerator. And I'm just wondering, does that have any affect on the refrigeration itself? If the tissue just went directly into the refrigerator, not in formalin, it would be cooled -

MR. HEWLETT:

A. Um-hm.

EATON, Q.C.:

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Q. - to 4 degrees I think is what you said. If it's in formalin, does that affect refrigeration at all?

MR. HEWLETT:

A. Yes, it cools faster, however that is not the point.

EATON, Q.C.:

Q. The point, I think, is that it doesn't count towards fixation, is that -

MR. HEWLETT:

A. No.

EATON, Q.C.:

Q. But it doesn't have any impact on the refrigeration aspect of it.

MR. HEWLETT:

A. It cools it slightly faster.

EATON, Q.C.:

Q. Okay. So -

MR. HEWLETT:

A. It would be best, if one were going to do that, to pre-cool the formalin. Heat transfer in a liquid mass, from a solid to a liquid is about 12 times faster. So, if you pre-cool the formalin solution, drop the warm tissue into it, it will cool 12 times faster than if

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you just sit it in a basin and leave it out in the refrigerator air. There are other side effects on the formalin, it tends to precipitate out and a number of other nasty things happen to it, but it doesn't fix. If you were going to deal with it, you can certainly cool it and formalin would be the way to cool it, certainly cool it more rapidly by placing it in a mass of formalin, but within these stated time periods, one would then have to deal with the specimen and that was really the issue. You can't just drop it in there and leave it.

EATON, Q.C.:

Q. I understand, I'm just wondering whether it had any negative impact by the fact that it was in formalin as compared to directly in the refrigerator. But it wouldn't negatively impact -

MR. HEWLETT:

A. No -

EATON, Q.C.:

Q. Could positively impact -

MR. HEWLETT:

A. Could positively impact.

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EATON, Q.C.:

Q. Another question that you made reference to in your report, there were two different substitutes for xylene used at the two different sites. And you made some comments about those and the fact that they have not been, I guess, properly tested or established as suitable substitutes.

MR. HEWLETT:

A. We do--no, I think probably suitable substitutes, they function as a substitute. What's in question is what is the effect on immunohistochemistry? The recommendations by the ad hoc committee will say is that if you are using a non-conventional reagent of any kind, that you have to run in parallel with a conventional reagent. The same samples over a hundred cases for ER and test it, only then--it may well be fine, but the point I was making is it's untested at the moment and nobody knows. And certainly the immunohistochemistry lab needs to know because if they're going to accept that specimen, they need to run a control with it that's been processed and checked in the same manner.

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EATON, Q.C.:

Q. Um-hm. Now, I don't know if that was ever done. Do you know if that was ever done?

MR. HEWLETT:

A. Not to my knowledge.

EATON, Q.C.:

Q. So, did you inquire--this is something that has come up, so I'm asking, did inquire -

MR. HEWLETT:

A. I didn't pursue it. I was looking at the stated practice.

EATON, Q.C.:

Q. Okay.

MR. HEWLETT:

A. If somebody has done it, then fine, I would withdraw the comment.

EATON, Q.C.:

Q. We just need to understand, sort of, the extent of what you're saying and -

MR. HEWLETT:

A. We're looking--and that's why the compliance issue is always at the end. We're looking specifically at breast at the moment, but our view is somewhat wider than that because we're thinking of the future. You don't want to

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repeat this issue in two or three years over some other marker, I assume.

EATON, Q.C.:

Q. No, I think that most of here would rather not, as interesting as it's been.

The next question that I have relates to, actually to each of the reports you prepared for Western and for Gander dealing with the drying of the slides. With respect to Western you made comment about the hot air oven at 100 degrees.

MR. HEWLETT:

A. Yeah.

EATON, Q.C.:

Q. And with respect to Gander, the use of the domestic microwave oven. Okay. And do I take it that you were referring to the slides being prepared for some other IHC, not for the ER/PR?

MR. HEWLETT:

A. For anything, any kind of staining. After the sections are cut, they're mounted on glass slides and put in a drying oven. The idea being to bond the section to the glass, dry it.

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EATON, Q.C.:
Q. Okay. And you made a comment again in each, that more preferably or it would be preferable to ship the blocks.
MR. HEWLETT:
A. For immuno.
EATON, Q.C.:
Q. For immuno?
MR. HEWLETT:
A. Yes.
EATON, Q.C.:
Q. Right.
MR. HEWLETT:
A. Most reference immuno labs prefer you send them the blocks because--I'll give you a simple example. If Corner Brook's routine section thickness is 5 micrometres, and they cut the sections at that, the routine section thickness in the immuno reference lab may be 3 micrometres. That's a significance difference in the amount of material on the slide and that affects the entire immuno staining process, particularly a semi-quantitative thing like ER, HER2 and -
MR. PARKS:

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A. If I may interject, we are a reference lab for Eastern Ontario for all of the ER/PR and HER2/neu and we will not handle slides. We only handle blocks to ensure total, that it's handled exactly the way our controls are.
EATON, Q.C.:
Q. Which I think the evidence has been, but that's what's done, the blocks are sent for the ER/PR and HER2/neu.
MR. HEWLETT:
A. But that's not what I was in -
EATON, Q.C.:
Q. Well, which is--what raises the question as to whether or not you were talking about other IHC or just -
MR. HEWLETT:
A. Any kind of IHC, any kind of IHC. I wasn't just asking about breast, in this case.
EATON, Q.C.:
Q. Okay.
MR. HEWLETT:
A. They have a procedure for immunohistochemistry, you know, special stains, unstained H&E.
EATON, Q.C.:

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Q. Which leads me, I guess, to the comment that or some of the comments that you made with respect to the state of the blocks in St. Anthony. And you talked about the tissue being dried out, I think, in some of the blocks that you looked at.
MR. HEWLETT:
A. Um-hm.
EATON, Q.C.:
Q. If, perhaps to you, Mr. Parks, if you received a block like that, that was part of the reference material, what would happen to it? Would you proceed with it? Would you send it back?
MR. PARKS:
A. I would probably call and ask how the block had been processed. And if I knew, like, on all of our documentation, fixation time, if I knew fixation time was adequate, I would proceed to take the block back through the system and reprocess it with proper solvents to produce a block that would give me better results.
EATON, Q.C.:
Q. So, if you would raise it with the lab that

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had sent it to you -
MR. PARKS:
A. I would call them and ask, oh yeah, I would call and ask them for sure.
EATON, Q.C.:
Q. That would be a reasonable expectation.
MR. PARKS:
A. Definitely. I would not accept something like that without a call to find out if something happened in transit because sometimes in transit some of these blocks get thrown in courier's cars and they're sitting in the heat. And in that case I would just simply have to re-embed it, but if they had told me that that's the way it looked, I would go back through the process.
MR. HEWLETT:
A. The other issue with that, if I may interject, is if the block is sunken in the, the person who is going to re-cut that block for immunohistochemistry has no idea where the lesion is in that block. And if you did nothing, you would have to simply shave away, shave away, until you got a complete section. You may have removed the area of tumour, the

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only area of tumour in the block. So I mean, it's poor technique. The very least a lab would do would be to actually melt that block down and flatten it, okay, so they could cut a complete section and they'd notify the lab and say "look, we're going to melt it down and re-embed it" not reprocess necessarily, but re-embed.

EATON, Q.C.

Q. And I think just one final question, and you made some comments about the state of the microscopes in St. Anthony. Did you make any inquiries of them as to what, if anything, was being done about that?

MR. HEWLETT:

A. Yes, I did, as a matter of fact, and they had been assured that there were some new--one or two new scopes apparently coming in.

EATON, Q.C.:

Q. Okay, on order and on route apparently.

MR. HEWLETT:

A. I guess.

EATON, Q.C.:

Q. Okay. Thank you. Those are my questions.

THE COMMISSIONER:

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Q. Thank you, Mr. Eaton. Ms. Newbury, do you have any questions? May I ask just your estimate of time, just because we've been here for a while and people might have a break if you are going to be a long period of time?

MS. NEWBURY:

Q. I have one small area, probably five minutes.

THE COMMISSIONER:

Q. Okay, if that's what it is, why don't we press on.

MR. BRYAN HEWLETT AND MR. WILLIAM PARKS, EXAMINATION BY MS. JENNIFER NEWBURY

MS. NEWBURY:

Q. Good afternoon. Jennifer Newbury, I represent the Canadian Cancer Society, and I just want to ask you about one small area this afternoon. Mr. Coffey made reference to some retesting taking place at Mount Sinai on DAKO equipment and he referenced some conversions of results from negative to positive. There's also been some evidence about what have been termed retroconversions. So these are conversions from positive results to negative results. Now the focus of retesting was not on the tests that were originally positive

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here in St. John's. So it was a fairly small group of positive results that were retested. There has also been some evidence that the explanation for perhaps some and maybe most of these retroconversions has been over calling of the slide due to background staining, and I'm wondering if, keeping in mind the scope of your review here in September and October, did you see anything in your review that could, aside from over calling due to background staining, that might contribute to an inaccurate false positive result? Is there anything in sort of the pre-analytical phase that might cause you any concerns about that type of a result?

MR. HEWLETT:

A. Difficult question to answer. I go back to one of my original remarks. There are two different antibodies and two different systems in use here. Mount Sinai runs a validated system. I happen to know that, and so one can believe their results. However, it could well be that that particular or those particular samples were incompletely fixed and this time the damage occurred to the 6F11 clone whereas

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the 1D5 clone was successful in attaching. So maybe both results could be real in the true sense. So the original staining, as reported as positivity, could be real. The new retest could also be real with that antibody. There are differences in sensitivities between these antibodies. That could account for it. It's a low number, but it could account for it.

MS. NEWBURY:

Q. In terms of relating those, I guess, equally valid results, I guess, to the patient themselves, which would be accurate, given that type of hypothetical explanation -

MR. HEWLETT:

A. Oh, dear!

MS. NEWBURY:

Q. When you say true, both of them are true results, but the patient, I guess, is one or the other?

MR. HEWLETT:

A. This, of course is - this, of course, is the dilemma we face. If we were to have two validated systems operating at their peak with different antibodies, and if we were to take a sample and run it with both antibodies, and if

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we were to do that with a series of samples, you can statistically expect only probably around 95 percent concordance. There is an inherent error built in. It may be as low as 3 per error, it could be as high as 8, or somewhere in between there. That's an inherent sort of false negative rate with one of the other. Both are accurate in the accepted sense that they give meaningful results. It's only when you start to compare small individual cases, that is not likely to happen if the material is properly prepared. Then the sensitivities are very, very close.

MS. NEWBURY:

Q. Okay. So given, I guess, some of the observations you made about fixation in some of the random slides that you looked at, and knowing what you know from your review, are there any concerns about perhaps what was generated here in St. John's, or are the concerns about what was generated from Mount Sinai?

MR. HEWLETT:

A. I did not look at any earlier slides generated here in St. John's. I looked at -

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MS. NEWBURY:

Q. At the blocks.

MR. HEWLETT:

A. At the blocks.

MS. NEWBURY:

Q. Right.

MR. HEWLETT:

A. So it would be pure speculation on my part to say that, you know, part of the - I can certainly say that some of the blocks were inadequately processed for whatever reason.

MS. NEWBURY:

Q. Okay.

MR. HEWLETT:

A. I mean, the physical evidence of that is right there on the block. What had happened to them prior to them being put on the processor, I mean, I suppose you could look at the section and if there was sufficient morphological change you could attribute to poor fixation, alcohol fixation, and you may be able to comment on that, and I believe other people have, but what happens if it's in that sort of magic 10 to 12 hour fixation time frame where the morphological changes are so subtle that

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most people would never pick it up, and you'd say it looks okay, but molecular damage has occurred, that's what we're talking about.

MS. NEWBURY:

Q. Now I was focusing then on the possible explanations, aside from background staining. Is there anything that you might have concern, either what you saw, or generally speaking, in immunohistochemical testing that could exacerbate the background staining looking at the pre-analytical phase?

MR. HEWLETT:

A. Well, you're talking about the retest and the original?

MS. NEWBURY:

Q. Yes.

MR. HEWLETT:

A. I'm pretty sure, but don't quote me, that Mount Sinai uses an avidin block. So they have a blocking system built in for blocking endogenous biotin.

MS. NEWBURY:

Q. Uh-hm.

MR. HEWLETT:

A. I have not seen the protocol for the original

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slides in St. John's, but it's not unusual for breast tumours to express biotin and cytoplasm. That can give you a stain. Just because it's brown doesn't mean it's positive.

MS. NEWBURY:

Q. Uh-hm.

MR. HEWLETT:

A. But something will be brown in the cytoplasm. I doubt you'd want to call that ER positive. I mean, I think everybody knows it's a nuclear marker that the instructions are to ignore any such plasmic staining.

MS. NEWBURY:

Q. So the avidin block that you understand is being used by Mount Sinai would block the background staining?

MR. HEWLETT:

A. Cytoplasmic staining, yes.

MS. NEWBURY:

Q. So the absence of that may not have the same advantage of blocking the background staining, and, I guess, if there were any sort of problems in terms of interpretation, that might be an issue?

MR. HEWLETT:

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A. The other issue is I don't know what they were using here. I do know that at some point they had switched, I think, to an Envision, a polymer detection system, which is avidin biotin free. So that wouldn't be the issue.

MS. NEWBURY:

Q. Right, yeah, but the - one thing that I think was being used as labelled - LSAB labelled striptavidin biotin.

MR. HEWLETT:

A. Striptavidin biotin system and endogenous biotin is a distinct possibility.

MS. NEWBURY:

Q. Okay.

MR. HEWLETT:

A. But that would be present in the negative control as well.

MS. NEWBURY:

Q. If a negative control was used?

MR. HEWLETT:

A. Well, yeah.

MS. NEWBURY:

Q. And in the absence of a negative control -

MR. HEWLETT:

A. Well, if it were just an ER stain with no

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negative control, the first thing I would think about, and probably Bill too, oh, that looks like there's endogenous biotin and cytoplasm and we would then probably repeat either with a non-evident biotin system or put a block on it.

MS. NEWBURY:

Q. And the concept of over antigen retrieval, is that something that you would have any information about?

MR. HEWLETT:

A. Yes.

MS. NEWBURY:

Q. Just generally speaking, what would that -

MR PARKS:

A. Over retrieval can bring up - it continues - in conjunction with fixation, any time you do retrieval you've optimized. If you are over retrieving, you can be breaking bonds and creating things that can non-specifically tramp antibody.

MR. HEWLETT:

A. Or cross react.

MR. PARKS:

A. Or cross react, exactly, because when you

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break - when you go past the point in your retrieval of breaking just the bonds that were there from the formalin to allow the - basically what happens is when the molecules all bonded together, what you're doing is trying to release the formalin bond so that the molecule re-opens. It will never be exactly what it was, but you're trying to open up the area so that you can - so the antibody can recognize it. If you exceed this, you start to break other bonds down, and, therefore, other components can be twisted or make it so they look like the antigen or the epitopes you're going after, but it's not real. So over retrieval definitely can cause false positivity. It is a potential of it, yes.

MS. NEWBURY:

Q. Okay, and, I guess one method of guarding against that would be to optimize the technique?

MR. PARK:

A. Every technique you use has to be optimized.

MS. NEWBURY:

Q. And would using a negative control aid in

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guarding against that occurring as well, or are the controls effective in that sort of a setting?

MR. PARKS:

A. Negative control is -

MR. HEWLETT:

A. A proper one could be.

MR. PARKS:

A. Yes.

MS. NEWBURY:

Q. And what would be a proper negative control?

MR. HEWLETT:

A. A true negative control consists of an antibody that is directed against something which is not in human material preferably. For example, fungus is quite commonly used, aspergillus. So there is a monoclonal antibody which is directed against aspergillus niger and it should be the same type of immuno globulin as your primary antibody is. So if your ER is an IGGIA, you need a negative control which is an IGGIA, but it's directed against aspergillus, not with anything human.

MS. NEWBURY:

Q. Uh-hm.

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MR. HEWLETT:
A. And you would substitute that in place of your ER primary antibody. That's a true negative control.
MS. NEWBURY:
Q. Uh-hm.
MR. HEWLETT:
A. A direct substitution of one antibody for another which should not react.
MS. NEWBURY:
Q. Okay.
MR. HEWLETT:
A. Under those circumstances, yes, it would pick it up because it's non-specific binding of the immuno globulin into probably the histones and the nucleus.
MS. NEWBURY:
Q. And is that type of a true negative control ever used for ER/PR testing?
MR. HEWLETT:
A. Should be.
MS. NEWBURY:
Q. On a routine basis?
MR. HEWLETT:
A. Yeah.

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MS. NEWBURY:
Q. Or just - not just during the optimization of the technique, but actually -
MR. HEWLETT:
A. Particularly if you're using a kit. They usually come with a true negative control built in.
MS. NEWBURY:
Q. Okay. Thank you very much. Those are all the questions I have.
THE COMMISSIONER:
Q. Do you have any questions, Ms. Chaytor?
MS. CHAYTOR:
Q. I have nothing, thank you.
THE COMMISSIONER:
Q. Anything arising, Mr. Coffey.
COFFEY, Q.C.:
Q. No, Commissioner.
THE COMMISSIONER:
Q. Thank you. Then it's only left for me to thank both of our witnesses. For me, it's been a really interesting day. I do appreciate you coming to assist us. I wish you all a Happy Thanksgiving. We'll see you on Tuesday morning. I'll remind you we're starting a half an hour early on Tuesday morning.

Upon conclusion at 5:31.

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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 10th day of October, 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 10th day of October, A.D., 2008

Judy Moss

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