Q. AND YOU SAY THAT BECAUSE OF THIS LINE HERE THAT SAYS "NONE"?
A. RIGHT.

Q. AND IT'S JUST BELOW THE LEVEL OF TWO HERE ON THIS FIGURE.
A. THAT'S CORRECT.

Q. NOW, JUST ABOVE THAT, THERE IS THE LINE THAT HAS PLUS NINE
ON IT.
A. RIGHT.

Q. WHAT DOES THAT REFER TO?
A. THAT WOULD REFER TO DOING THE EXPERIMENT IN THE PRESENCE OF
THE 9-MER, THE NONANUCLEOTIDE, AND SEE WHAT THE LEVEL OF
INCORPORATION WAS WHEN YOU USED A TWO-FOLD EXCESS OF THE
NONAMER.

Q. AND HOW MANY C'S SHOULD THAT NINE-BASE PAIR PRIMER FILL IN
IF IT STARTS HERE AND EXTENDS TO THE END?
A. WE CAN COUNT IT OUT THERE, OBVIOUSLY, HOW MANY IN THIS
PARTICULAR CASE, TO MAKE SURE I DON'T MISCOUNT AGAIN.

(PAUSE IN PROCEEDINGS)

THE WITNESS: SIX. I THINK THAT'S SIX?

Q. (BY MR. PASAHOW) YES.

SO THEY FOUND THAT, ON AVERAGE, IT WENT ABOUT A THIRD
OF THE WAY?

A. I'M NOT SAYING IT WENT A THIRD OF THE WAY. PROBABLY A
CERTAIN NUMBER OF THE MOLECULES COMPETED OUT.

THERE ARE TWO DIFFERENT THINGS ONE HAS TO KEEP IN MIND.

EITHER WE CAN GET NOT COMPLETE FILL-OUT, OR YOU CAN GET
COMPETITION OF ONE PARTICULAR SEGMENT WHERE THE PRIMER WOULD ANNEAL CORRECTLY AND IT WOULD NOT FILL OUT COMPLETELY, BUT IT JUST DEPENDS ON HOW MANY MOLECULES WILL DO THAT.

Q. AND THE ONLY WAY TO FIND OUT WHICH YOU GOT IS TO DO SOME SORT OF ANALYSIS OF THE PRODUCT.

A. THAT'S CORRECT.

Q. NOW, YOU RECALL THAT DR. MOLINEUX TESTIFIED THAT HE DID AN EXPERIMENT WITH THE NINE-BASE PRIMER AND DNA-II EXCEPT HE USED 10 TIMES EXCESS OF THE PRIMER OVER THE DNA-II TEMPLATE?

A. ONE PRIMER OR TWO PRIMERS?

Q. ONE PRIMER --

A. ONE PRIMER.

Q. -- DOUBLE-STRANDED TEMPLATE.

A. YES. UH-HUH, YES.

Q. AND HE DID THAT WORK WITH A 10 TIMES EXCESS OF --

A. YES.

Q. -- THE NINE-BASE PRIMER OVER THE DNA-II TEMPLATE.

A. (NODDING HEAD.)

Q. AND DO YOU RECALL HE TOLD US THAT STILL 70 SOME PERCENT OF THE TIME HE WAS UNABLE TO GET THE NINE-BASE PRIMER TO EXTEND?

A. WHAT HE SAID WAS THAT HE WOULD SEE 27 PERCENT INHIBITION OF THE PRIMER EXTENSION COMPONENTS IN THE HAIRPIN FORM, BUT THAT REACTION ONLY OCCURRED TO ABOUT 35 TO 40 PERCENT TOTALLY. SO IT'S -- IN ESSENCE, HE SAW ONLY 70 PERCENT OF 40 PERCENT.

Q. WHAT HE SAW WAS VERY LITTLE INCORPORATION RESULTING FROM THE
PRIMER EXTENDING ON THE TEMPLATE?

A. NO, NO. I'M NOT SAYING THAT.

WHAT HE TESTIFIED TO WAS THAT HE SAW AN INHIBITION OF
THE HAIRPIN EXTENSION TO THE LEVEL OF 27 PERCENT.

Q. UH-HUH.

A. AND THE HAIRPIN LEVEL OF EXTENSION WAS ONLY 40 PERCENT.

Q. WELL, WHAT HE -- WHAT HE SAW WAS THAT 70 PERCENT OF THE TIME
THE HAIRPIN EXTENSION WOULD TAKE PLACE.

A. NO, THAT'S NOT WHAT HE SAID AT ALL. HE SAID IF YOU
CALCULATE 70 PERCENT OF 40, THAT'S ABOUT 30 PERCENT, SO THAT
WOULD MEAN THAT 30 PERCENT OF THE TIME THE HAIRPIN EXTENSION
WOULD TAKE PLACE; THE OTHER 70 PERCENT OF THE TIME THE PRIMER
EXTENSION WOULD TAKE PLACE. THAT'S WHAT HE SAID. IT WAS AN
INHIBITION OF THE HAIRPIN WHICH ONLY OCCURRED TO 40 PERCENT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, IN -- IN THIS CHART, HOW LONG DID DR.
KLEPPE LET THE NINE-BASE PRIMER TRY TO EXTEND ON THE . . .

DNA-II SINGLE-STRAND?

A. OH, AS IT SHOWS, 120 MINUTES. TWO HOURS.

Q. TWO HOURS.

AND HE STILL GOT ABOUT A THIRD OF THE NUMBER OF BASES
INCORPORATED THAT HE THOUGHT HE SHOULD.

A. YES. IN THE SAME TIME, IN TWO HOURS, HE WILL GET COMPLETE

Q. WHAT DID YOU JUST SAY ABOUT THE 16, 12 AND 20? I'M SORRY.
A. Okay. When he added the excess, only the two-fold excess of the 16, the 12, and the 20, he --

Q. That's these lines?

A. That's right.

Q. Uh-huh.

A. In the same time period, he would get a leveling off at the levels which I indicated in that particular paper.

Q. And that's somewhere around four?

A. Four and --

Q. Five?

A. Yes. You can just count out how many we would require for the 12 and the 16 and the 20.

Q. How many is that?

A. Oh, I have to just look at it again and count, Mr. Pasahow.

(PAUSE IN PROCEEDINGS)

THE WITNESS: I think it's four for the 12; it's four for the 16; and it's four for the 20.

Q. (By Mr. Pasahow) If it's four for each, why are these lines separated here?

A. Might be slight variation again in pipetting and set-up of reaction. I think it was, you know, in 1969, 1970, that probably was the experimental error.

Q. So it would be impossible, given the level of experimental error, to be able to distinguish between these three here?

A. I think they're very close, yes.
Q. AND THESE TWO, OF COURSE, ARE EVEN CLOSER, SO IT WOULD BE IMPOSSIBLE, GIVEN THE EXPERIMENTAL ERROR --
A. MIGHT BE. MIGHT BE, YES.
Q. IF I MIGHT FINISH.

IT WOULD BE IMPOSSIBLE, GIVEN THE EXPERIMENTAL ERROR, TO TELL THE DIFFERENCE BETWEEN USING THE NINE-BASE PRIMER IN EXTENDING IT AND THE RESULT YOU'D GET IF YOU JUST GOT THE HAIRPIN WITHOUT ANY PRIMER.
A. YEAH, BUT AS DR. MOLINEUX TESTIFIED, HE INDICATED THE FIGURES ON THAT, THAT HE SAW 27 PERCENT INHIBITION.
Q. DID DR. MOLINEUX TESTIFY ABOUT THIS EXPERIMENT?
A. NO, NO.
Q. I JUST MISSED THAT.
A. YOU JUST ASKED ME BEFORE ABOUT THIS EXPERIMENT. IT WAS THE DUPLEX II AND THE ONE PRIMER. SO I'M RELATING THAT ALSO BECAUSE I HAVE NUMBERS ON THAT EXPERIMENT.
Q. THIS IS DR. KLEPPE'S EXPERIMENT.
A. THAT'S CORRECT.
Q. AND DR. KLEPPE AND DR. KHORANA PUBLISHED THIS EXPERIMENT.
A. THAT'S RIGHT.
Q. AND WHAT WE'RE SAYING IS, BECAUSE OF EXPERIMENTAL ERROR, IT WOULD BE IMPOSSIBLE TO TELL THE DIFFERENCE IN THE PUBLISHED DATA BETWEEN USING THE DNA-V HAIRPIN STRUCTURE IN EXTENDING IT AND THE RESULTS YOU'D GET IF YOU USED THE NINE-BASE PRIMER ON THAT SAME HAIRPIN AND EXTENDED IT.
A. AS I INDICATED BEFORE, THERE'S VERY LITTLE DIFFERENCE, YES.
Q. AND THAT DIFFERENCE IS LESS THAN THE EXPERIMENTAL ERROR.
A. MIGHT BE, YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, GIVEN THESE RESULTS, WOULD YOU AGREE
THAT, IN -- IN EXPERIMENT NINE AND IN EXPERIMENT 28, SOME OF THE
PRODUCT BEING MADE MUST HAVE BEEN RESULTING FROM THIS HAIRPIN
EXTENDING ON ITSELF?
A. I THINK THERE'S SEVERAL ASPECTS TO CONSIDER THERE. I THINK
WHEN ONE STARTS PUTTING IN TWO PRIMERS, WE'RE NOW LOOKING AT
DUPLEX FORMATION, WE USE A PRIMER RATIO, WHICH HE USED,
10-TO-ONE PRIMER-TO-TEMPLATE RATIO, THAT WE ARE NOW OBVIOUSLY
GOING TO GET BETTER COMPETITION THAN THE TWO-TO-ONE EXPERIMENT
WHICH HE SHOWED IN FIGURE 13 OF THE KLEPPE PAPER.

WE'RE LOOKING AT THE STRUCTURE WHICH YOU SHOWED THERE
ON THE TOP PART OF THAT FIGURE, WHERE YOU SHOWED FIVE OF THE
BASE PAIRS ARE HYDROGEN BONDED.

OKAY. I'M NOT COUNTING THE C, BECAUSE THE C ISN'T
HYDROGEN BONDED, WHILE IF I PUT IN THE PRIMER, THE C NONAMER,
I'M LOOKING AT EIGHT BASES WHICH ARE HYDROGEN BONDED. I'M
LOOKING AT A MORE STABLE COMPLEX IN THE PRESENCE OF THE PRIMER.

THE SECOND PART IS THAT I CAN -- AND THIS MIGHT BE A
LITTLE DIFFICULT ARGUMENT TO FOLLOW -- IS, WE HAVE TO LOOK AT
THE ASPECT OF THE REACTION THAT THE FORMATION OF A HAIRPIN IS
ONE DUPLEX FALLING BACK ON ITSELF AS YOU SHOW THERE. THIS IS
WHAT IS NORMALLY REFERRED TO IN THE KINETICS AS A UNIQUE MOLECULAR REACTION, ONE MOLECULE REACTING WITH ITSELF.

OKAY. BY DEFINITION A UNIMOLECULAR REACTION IS CONCENTRATION-INDEPENDENT. WHEN I START LOOKING AT THE INTERACTION OF ONE STRAND WITH ANOTHER STRAND, THERE'S TWO MOLECULES COMING TOGETHER. THIS IS WHAT IS REFERRED TO AS A BIMOLECULAR REACTION, AND THIS PARTICULAR ONE IS CONCENTRATION-DEPENDENT.


THE THIRD PART OF THAT IS THAT, IN THIS HAIRPIN, IF THIS HAIRPIN IS EXTENDED, IT BECOMES, IN ESSENCE, A DEAD MOLECULE IN THE REACTION. IT CANNOT PARTICIPATE ANY MORE BECAUSE NOW THERE'S A STABLE STRUCTURE THAT YOU CANNOT COMPETE IT OUT.

SO THERE ARE THREE FACTORS I THINK TO CONSIDER HERE.

Q. THE QUESTION, SIR, WAS: IN EXPERIMENT THREE AND IN EXPERIMENT NINE, WHERE THESE HAIRPIN STRUCTURES WERE PUT IN, WOULD YOU EXPECT SOME OF THE PRODUCT TO BE THIS EXTENSION REACTION?

A. FIRST OF ALL, IN EXPERIMENT THREE AND NINE, HAIRPIN
Structures were not put in. A duplex was put in.

The duplex was denatured in the presence of a 10-fold excess of primer, which is very different from what is described here where they used a two-fold excess of primer. There is a fine chance that some hairpin might form, that’s correct.

Q. So -- just so that I’m clear, the answer to my question is, yes, you would expect that, in experiment three and nine, some of the product that results would result from the hairpin extension.

A. There is a chance of hairpin formation there, yes.

Q. Now, the way to find out whether you’ve got the hairpin extension or whether you’ve got the nine-base primer extending is, you’d analyze the product with nearest neighbor analysis.

A. That’s correct.

Q. And, of course, you’ve told us that wasn’t done for experiments nine or 28.

A. That’s right.

(Pause in proceedings)

Q. (By Mr. Pasahow) Now, in addition to this what you’ve referred to, I guess, as one molecule or intramolecular structure --

A. Unimolecular, yes.

Q. -- you can get other kinds of structures out of this; is that right?

A. Yes.
Q. AND, IN FACT, DR. KLEPPED DESCRIBED THAT TO THE GROUP AS WELL.
A. YES.
Q. AND THAT IS THIS THING HERE WITH A BIT OF A BUBBLE IN THE MIDDLE.
A. THAT'S RIGHT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) AND IN THIS STRUCTURE, EACH OF THE TWO ENDS ARE THREE-PRIME ENDS AND SO THEY'D BE ABLE TO EXTEND AS WELL.
A. YOU WILL GET THE SAME LEVEL OF INCORPORATION. YOU WOULD SEE FOUR C'S GOING IN IN BOTH STRANDS.
Q. AND THAT'S A TWO-MOLECULE REACTION.
A. RIGHT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, IN THE KLEPPED PAPER, WHERE DR. KHORANA AND DR. KLEPPED DECIDED TO PUBLISH SOME OF THE RESULTS FROM USING A STRANDED DNA-II, THEY ACCOMPANIED IT WITH NEAREST NEIGHBOR ANALYSIS.
A. THAT'S CORRECT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, THE BOTTOM STRAND OF DNA-II, OF COURSE, FORMS A HAIRPIN, TOO.
A. THAT'S RIGHT.
Q. AND YOU'VE ALREADY TOLD US THAT, IN THIS STRUCTURE, WE WON'T
GET ANY EXTENSION THIS WAY EVEN IF THE ENZYME CUTS THAT OFF
BECAUSE IT'S THE WRONG END.
A. RIGHT.
Q. AND THE QUESTION HERE IS: WHEN YOU PUT ON A 10-BASE PRIMER
AND IT COMES UP AGAINST THIS END, WHAT HAPPENS?
A. I MEAN, IT COULD EITHER PUSH IT AWAY OR IT WOULD STOP.
Q. OR ANOTHER POSSIBILITY IS THAT IT WOULD START CHOPPING OFF
THOSE BASES?
A. THAT'S A POSSIBILITY BUT NOT AT THAT PARTICULAR PH DR.
KLEPPE WAS WORKING, BECAUSE HE WAS WORKING AT PH 6.9. AT PH
6.9, THERE IS NO FIVE-PRIMER EXONUCLEASE ACTIVITY IN THE ENZYME.
Q. THERE WAS NONE, OR IT'S INHIBITED?
A. IT'S INHIBITED. IT'S COMPLETELY INHIBITED.

(PAUSE IN PROCEEDINGS)
Q. (BY MR. PASAHOW) SO EITHER IT WOULD COME TO THE END HERE,
YOU THINK, AND STOP, OR IT WOULD COME TO THE END AND SOMEHOW
PUSH IT OUT OF THE WAY?
A. THAT'S A POSSIBILITY.
Q. NOW, THAT EXPERIMENT WAS DONE AS WELL; IS THAT RIGHT?
A. UH-HUH, YES.
Q. AND THAT WAS REPORTED BY DR. KLEPPE AND DR. KHORANA IN THEIR
ARTICLE.
A. THAT'S RIGHT, IN FIGURE 14 OF THE KLEPPE PAPER.

(PAUSE IN PROCEEDINGS)
Q. (BY MR. PASAHOW) I HAVE A BLOWUP OF FIGURE 14 HERE MARKED
AND WHAT WE'RE TALKING ABOUT IS THIS LINE HERE WITH --

THAT'S CALLED DECA?

A. UH-HUH.

Q. AND DECA IS THE WORD FOR 10?

A. 10, YES.

Q. AND IT SEEMS TO INDICATE HERE THAT HE WAS GETTING ABOUT SIX SPACES INCORPORATED?

A. THAT'S RIGHT.

Q. AND THAT WOULD BE SIX C'S?

A. YES. HE WAS MEASURING C'S, I THINK, ON THIS ONE, YEAH.

Q. IF IT WENT ALL THE WAY TO THE END, HOW MANY C'S WOULD HE GET?

(PAUSE IN PROCEEDINGS)

THE WITNESS: I THINK IT WAS SEVEN.

Q. (BY MR. PASAHOW) ARE YOU REMEMBERING TO COUNT THIS ONE BACK HERE AT THE BEGINNING?

A. NO, I DIDN'T ADD THAT ONE. I WAS JUST LOOKING AT THE EXTENSION, BECAUSE I THOUGHT YOU STARTED WITH SEPARATED STRANDS, AND I CAN'T RECALL WHETHER THE STRANDS WERE FILLED OUT OR . . .

Q. IF YOU LOOK AT FIGURE 14, I THINK IT SHOWS THERE'S A FILL-IN --

A. THERE IS, THAT'S RIGHT.

Q. -- HERE AS WELL AS HERE.

A. BUT YOU ASKED ME ABOUT THE EXTENSION OF THE DECANUCLEOTIDE,
AND THAT'S SEVEN.

Q. SO THE NUMBER THAT WE WOULD HAVE GOTTEN IN PERFORMING THE
REACTION SHOWN HERE IN FIGURE 14, IF IT HAD GONE ALL THE WAY, IS
EIGHT.

A. THAT’S CORRECT.

Q. AND, INSTEAD, THEY GOT A LITTLE LESS THAN SIX.

A. RIGHT.

Q. OR ABOUT 75 PERCENT.

A. RIGHT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) AND THAT, OF COURSE, IS WHAT THEY REPORTED
IN THE TEXT, THAT THE REACTION USING THE DECANUCLEOTIDE AS THE
PRIMER WENT TO ABOUT 75 PERCENT COMPLETION.

A. RIGHT. THAT’S RIGHT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, NOW THAT WE’VE HAD A CHANCE TO LOOK
AT THE PUBLISHED DATA ON DNA-II, I’D LIKE TO GO BACK THROUGH
SOME OF THESE EXPERIMENTS YOU TOLD US ABOUT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) AND WE’VE BLOWN THEM UP HERE SO THEY DON’T
GO QUITE SO FAST. STARTING WITH EXPERIMENT THREE, IT STARTS ON
B-227.

NOW, IN EXPERIMENT THREE, ONE OF THE THINGS THAT GETS
ADDED HERE IS WATER.

A. (NODDING HEAD.)
Q. WHY IS WATER ADDED?
A. I THINK TO BRING UP THE REACTION TO THE APPROPRIATE
CONCENTRATION.

Q. WHAT DO YOU MEAN BY THAT?
A. APPROPRIATE CONCENTRATION OF WHAT DR. KLEPP DESIGN THE
REACTION FOR.

Q. THAT IS, HE'D WANT A CERTAIN AMOUNT OF LIQUID THERE?
A. THAT'S CORRECT.

Q. AND DURING THE COURSE OF THE EXPERIMENT, TO KEEP THE
CONCENTRATION CONSTANT IF HE ADDED SOME OTHER THINGS, HE'D ADD
MORE LIQUID?
A. I MEAN, IF YOU ADD SOMETHING MORE, IT WON'T BE CONCENTRATE,
OF COURSE.

Q. BUT THE PURPOSE OF THE WATER IS TO SET A SPECIFIC
CONCENTRATION OF THE VARIOUS THINGS IN THERE?
A. HE WOULD SET UP THE REACTION THAT HE WOULD COME UP IN THIS
PARTICULAR CASE, SAY, VOLUME OF WHATEVER IT IS, 75 MICROLITERS,
LET'S SAY, SO THE LAST ADDITION HE WOULD MAKE WOULD BE ADDITION
OF WATER TO FILL IT OUT TO THAT PARTICULAR WAY YOU DESIGNED IT.
DESIGN WITH RESPECT TO THE CONCENTRATION OF THE TRIPHOSPHATES,
DESIGN WITH RESPECT TO THE CONCENTRATIONS OF DUPLEX AND PRIMERS.

Q. NOW, HE GOES THROUGH THAT, AND HE DOES THIS FILL-OUT, AND
THEN HE DOES -- HE STARTS DOING HIS CONTROLS.
A. UH-HUH.

Q. AND THE FIRST OF THOSE CONTROLS WERE EXPERIMENTS FOUR, FIVE
A. YES.

Q. -- THAT YOU SHOWED US.

AND AS I RECALL IT, EXPERIMENT FOUR INVOLVED PUTTING IN THE DNA-II AND HEATING IT?

A. THAT'S RIGHT.

Q. AND EXPERIMENT FIVE INVOLVED PUTTING IN THE DNA-II AND NOT HEATING IT.

A. THAT'S CORRECT.

Q. AND HE GOT A BIT MORE WHEN HE DID NOT HEAT IT THAN WHEN HE DID HEAT IT.

A. THAT'S RIGHT.

Q. WHY IS THAT?

A. I'M NOT EXACTLY SURE. I THINK IN THE EXPERIMENT NUMBER FIVE, HE OBVIOUSLY STARTS WITH HIS PREFORMED DUPLEX. IN EXPERIMENT NUMBER FOUR, HE TAKES A PREFORMED DUPLEX AND, IN ESSENCE, YOU KNOW, PULLS THE STRAND APART. AND NOT ALL OF IT COMES BACK THE WAY WE, OF COURSE, HAD THE STARTING MATERIAL, YES.

Q. SURE. ONCE YOU PULL IT APART BY HEATING IT, THE HAIRPINS HAVE A CHANCE TO FORM.

A. THEY DEFINITELY HAVE A CHANCE TO FORM, YES.

Q. AND ALSO THOSE LOOPING STRUCTURES AND OTHER THINGS COULD FORM.

A. YES, YES.
Q. IS THAT RIGHT?
A. THAT'S CORRECT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, THE POINT OF EXPERIMENT FOUR WAS TO SEE IF HE WAS GETTING THE INCORPORATION OF THE TWO C'S ON THE END. WAS THAT THE POINT OF THE CONTROL?
A. THAT'S ONE OF THE POINTS. THE OTHER POINT IS TO SEE WHETHER ANYTHING ELSE HAPPENED, OBVIOUSLY, AFTER YOU WENT THROUGH DENATURATION STEP.

Q. NOW, DOES EXPERIMENT FOUR TELL HIM WHETHER OR NOT HE'S GETTING THE HAIRPINNING?
A. NO, IT DOES NOT.

Q. AND THAT'S BECAUSE, IF HE GOT THE HAIRPIN, HE'D GET TWO C'S INCORPORATED.
A. NO. IF HE HAD THE HAIRPINS, HE GETS FOUR C'S INCORPORATED.

Q. WELL, THEORETICALLY, HE'D GET FOUR, BUT WHAT HE FOUND EXPERIMENTALLY WAS THAT HE GOT TWO; ISN'T THAT RIGHT?
A. WHEN HE SHOWED IT IN THE EXPERIMENT, YES, BUT, THEORETICALLY, YOU WOULD GET FOUR. YOU CAN GET AS MANY AS FOUR.

Q. LET'S GO BACK TO THE DATA THAT GOT PUBLISHED HERE.
A. YES.

Q. WE'RE TALKING ABOUT THIS LINE HERE, SAME PIECE OF DNA, WITH NO PRIMER.
A. IT'S NOT THE SAME PIECE OF DNA. THAT'S A SEPARATED STRAND.
Q. YES.
A. THE OTHER CASE, WE START WITH A DUPLEX.

Q. YES.

A. IT'S VERY DIFFERENT.

Q. BUT WHEN THE SINGLE-STRAND EXTENDED, WHAT DR. KLEPPE FOUND WAS IT TENDED TO GET, ON AVERAGE, TWO C'S INCORPORATED.

A. AS I SAID, WHEN HE WOULD START WITH A SEPARATED STRAND. IF HE STARTS WITH A DUPLEX, THOSE STRANDS, OF COURSE, HAVE A GOOD OPPORTUNITY TO COME BACK TOGETHER AGAIN.

Q. I'M NOT SURE I GOT AN ANSWER, YES OR NO, TO THE QUESTION.

WHEN DR. KLEPPE STARTED WITH A SEPARATED STRAND, THE TOP STRAND OF DNA-II, AND FORMED -- IT FORMED THE HAIRPIN, HE GOT TWO C'S INCORPORATED.

A. YES, THAT'S CORRECT.

Q. AND THAT'S NOTWITHSTANDING THE FACT THAT YOU POINT OUT IT THEORETICALLY COULD GET FOUR.

A. YES.

Q. NOW, THE BOTTOM-STRANDED DNA-II, IF IT FORMS THE HAIRPIN, GETS ZERO.

A. YES.

Q. SO IF THE STOP STRAND DID WHAT THIS CHART SHOWS AND GOT TWO --

A. UH-HUH.

Q. -- AND THE BOTTOM STRAND GOT ZERO, IF BOTH STRANDS FORMED THEIR HAIRPINS, YOU'D WIND UP WITH TWO C'S INCORPORATED.

A. NO. I DON'T FOLLOW THAT.
Q. THE STOP STRAND GETS TWO C'S INCORPORATED FROM ITS HAIRPIN.
A. THE AMOUNT HE OBSERVED WAS TWO, YES.
Q. YES.
A. YES.
Q. AND THE BOTTOM STRAND GOT ZERO INCORPORATED FROM THE HAIRPIN.
A. YES. THEY BOTH GO TO THE TOP STRAND, YES.
Q. AND SO IF YOU GOT THE -- THE TOTAL OF THE TWO HAIRPINS FORMING --
A. UH-HUH.
Q. -- EXPERIMENTALLY IT WAS FOUND TO BE TWO.
A. YES.
Q. AND ALSO IF YOU FILL IN DNA-II AT THE TWO ENDS, YOU INCORPORATE TWO C'S.
A. THAT'S CORRECT.
Q. SO YOU GET THE SAME NUMBER --
A. YES.
Q. -- REGARDLESS.
A. YES.
Q. DID ANY OF THE OTHER CONTROLS THAT WERE RUN IN EXPERIMENTS FOUR, FIVE, SIX, SEVEN AND EIGHT HAVE A -- HAVE A CONTROL WHERE THE TWO-TEMPLATE STRANDS WOULD HAVE A CHANCE TO FORM A HAIRPIN?
(PAUSE IN PROCEEDINGS)
THE WITNESS: I DON'T THINK SO.
(PAUSE IN PROCEEDINGS)
Q. (BY MR. PASAHOW) LET'S GO TO EXPERIMENT NINE, THEN.

YOU TOLD US THAT DR. KLEPPE STARTED OUT BY JUST LETTING

THIS THING SIT THERE FOR TWO HOURS WITHOUT HEATING IT?

A. HE, IN ESSENCE, TOOK THE REACTION THREE, WHICH HE HAD WORKED

ON, YOU KNOW, A FEW DAYS BEFORE AND PUT ASIDE, AND THEN HE JUST

ADDED THE ENZYME AND LET IT SIT FOR UP TO 60 MINUTES, I THINK.

Q. TWO HOURS.

A. 60 MINUTES?

Q. I'M SORRY. ONE HOUR.

SO WHY -- WHY WOULD HE TAKE A REACTION THAT HE HAD

ALREADY FILLED OUT AND ADD MORE ENZYME AND LET IT SIT FOR AN

HOUR?

A. I GUESS IT WAS JUST ANOTHER CONTROL REACTION HE RAN TO MAKE

SURE NOTHING HAD HAPPENED.

Q. AND WHAT HE EXPECTED WAS, HE'D GET VERY LOW INCORPORATION.

A. HE WOULD EXPECT TO SEE VIRTUALLY THE SAME AS WHAT HE HAD

FINISHED WITH IN, YOU KNOW, THE END OF EXPERIMENT THREE.

Q. AND THAT'S WHAT HE GOT.

A. VERY CLOSE TO IT.

Q. NOW, I'D LIKE TO TALK ABOUT WHAT HAPPENS AS IT GOES THROUGH

 THESE NEXT ROUNDS.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) SORTED OUT, IT GREW A LITTLE BIT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) CAN YOU SEE THAT?
A. IT'S GOING TO TAKE ME AWHILE TO TAKE IT IN, MR. PASAHOW.

(PAUSE IN PROCEEDINGS)

THE WITNESS: YES.

Q. (BY MR. PASAHOW) STARTING OFF HERE AT THE TOP, THAT SHOWS THE BEGINNING WHERE WE JUST FILL IN THESE TWO RADIOACTIVE C'S.

AND SO AT THE END OF THAT, THERE'S INCORPORATED TWO RADIOACTIVE C'S AND WE'VE GOT OUR TWO C'S.

AT THE SAME TIME THAT'S GOING ON, THIS NEXT EXTENSION IS HAPPENING; RIGHT?

A. THAT'S CORRECT, BECAUSE DR. KLEPPE DID IT ALL AT THE SAME TIME.

Q. AND AS I GUESS WE'VE NOW DECIDED, HE FILLS IN 12 MORE RADIOACTIVE C'S --

A. RIGHT.

Q. -- AS EACH OF THESE GREEN PRIMERS EXTENDS DOWN THE TEMPLATE.

A. RIGHT.

Q. SO AT THE END OF EXPERIMENT THREE, HE'S INCORPORATED A TOTAL OF 14 --

A. RIGHT.

Q. -- C'S.

A. RIGHT.

Q. NOW, IF HE REALLY DID A PCR REACTION, WHAT WOULD HAPPEN IS WHAT'S SHOWN DOWN HERE, I THINK; IS THAT RIGHT?

A. I ABSOLUTELY AGREE WITH THAT.

Q. AND THIS TOP STRAND HERE WOULD COME DOWN HERE, THIS STRAND
WOULD COME HERE, THIS STRAND WOULD COME HERE, AND THIS STRAND
WOULD COME HERE.

A. RIGHT.

Q. AND EACH OF THEM WOULD HAVE A NEW PRIMER --
A. YEAH.

Q. -- AND EACH OF THEM WOULD GET EXTENDED.
A. YEAH. YOU WOULD SEE -- YOU WOULD EXPECT ABOUT THREE TIMES
AS MANY C’S.

Q. AND SO WE -- I COUNTED 24 GET INCORPORATED IN THIS CYCLE.
A. SO YOU WOULD GO FROM 14 TO 38, THAT’S CORRECT.

Q. NOW, DID DR. KLEFFE SEE ANYTHING LIKE THAT LEVEL OF
INCORPORATION?
A. NO. I DON’T THINK HE COULD SEE THAT MUCH BECAUSE HE ONLY
HAD AT THAT POINT ABOUT A FIVE-FOLD EXCESS OF PRIMER.

Q. NOW, IF INSTEAD OF THAT HE HAD MADE SOMETHING WHICH WASN’T
COMPLETE SO IT COULDN’T BE EXTENDED, AND HE JUST HAD HIS PRIMERS
COME BACK ON HIS ORIGINAL TEMPLATE IN EACH STRAND, AT THE END OF
THAT FIRST CYCLE, HE’D INCORPORATED ANOTHER 12 C’S AS HE WENT
THROUGH THE FIRST ROUND OF EXTENSION IN EXPERIMENT NINE; IS THAT
RIGHT?

A. I’M NOT FOLLOWING WHAT YOU’RE SAYING.

Q. LET’S SEE IF I CAN BE CLEARER:

IF IN EXPERIMENT NINE --

A. YES. 9-B YOU’RE TALKING ABOUT.

Q. YES.
A. YES.

Q. IF INSTEAD OF DR. KLEPPHE HAVING BEEN SUCCESSFUL IN
REPRODUCING THE ORIGINAL TEMPLATES --

A. UH-HUH.

Q. -- THESE THINGS HAD FORMED HAIRPINS IN OTHER THINGS, AND SO
THE ONLY TEMPLATE HE'S GOT IN THERE IS HIS ORIGINAL TEMPLATE NOW
IN 9-B --

A. UH-HUH, YES.

Q. -- AND HIS PRIMERS EXTEND JUST ON THAT ORIGINAL --

A. YES.

Q. -- TEMPLATE, THEN HE'D INCORPORATE 12 --

A. UH-HUH.

Q. -- MORE C'S IN ROUND 9-B.

A. YES.

Q. NOW, DID HE SEE THAT MUCH INCORPORATION; THAT IS, THE
RADIOACTIVITY THAT WOULD RESULT FROM ABOUT 12 MORE C'S BEING
INCORPORATED?

A. HE SAW SLIGHTLY LESS.

Q. LESS THAN HE WOULD HAVE HAD --

A. YES.

Q. -- IF HE'D JUST DONE A LINEAR REACTION.

A. YES.

Q. AND HOW ABOUT IN THE NEXT -- THE NEXT ROUND NOW:
IF HE DID PCR, AND HE WAS REALLY GETTING ALL OF THIS
HAPPENING, IN THE NEXT ROUND, HE'D INCORPORATE ANOTHER 48 C'S,
TWICE THIS NUMBER?
A. NO. IN THE NEXT ROUND, OBVIOUSLY, HIS PRIMER-TO-TEMPLATE RATIO KEEPS GOING DOWN AND DOWN, AND HE WILL EXPECT NOT TO GET THE SAME COMPLETION OF REACTION, JUST AS I WENT THROUGH EARLIER WITH DR. MOLINEUX'S EXPERIMENTS.

Q. IF -- IF DR. KLEPPE STARTED WITH A PRODUCT OF ROUND TWO --
A. RIGHT.

Q. -- AND HE USED THE PRODUCT OF ROUND 9-B AS TEMPLATE IN ROUND 9-C --
A. YES.

Q. -- AND EXTENDED IT, HE WOULD HAVE HAD 48 MORE C'S.
A. YES.

Q. AND SO HE THEN WOULD HAVE A TOTAL OF 96 RADIOACTIVE C'S.
A. 96, RIGHT.

Q. DID HE SEE THAT KIND OF INCORPORATION OF RADIOACTIVE C'S?
A. NO. IT WOULD HAVE BEEN IMPOSSIBLE TO SEE IT WITH THE -- YOU KNOW, AS I MENTIONED, WITH THE PRIMER AMOUNTS HE WAS USING.

Q. IN THAT THIRD ROUND, DID HE SEE THE NUMBER OF C'S THAT HE'D GET IF HE DID AN EFFICIENT LINEAR REACTION?
A. NO, HE DID NOT.

Q. SO IN EACH CYCLE OF EXPERIMENT 9-B AND 9-C, HE GOT LESS INCORPORATION THAN HE COULD HAVE GOTTEN BY DOING A LINEAR REACTION?
A. YEAH. BUT IF YOU REFERENCE THIS TO THE FIRST REACTION, REACTION THREE, WHERE HE SAW ABOUT A FIVE- TO SIX-FOLD INCREASE
IN THE RADIOACTIVITY OVER ONE OF THE CONTROLS, WHICH WOULD SUPPORT THAT HE WOULD SEE APPROXIMATELY 80 PERCENT OF THE 14 C'S WHICH WOULD BE INCORPORATED.

SO THERE WAS, IN OTHER WORDS, NOT ONLY EXTENDING ONE STRAND; IT WAS EXTENDING BOTH STRANDS.

Q. UH-HUH. WELL, THE WAY WE KNOW WHETHER OR NOT HE WAS USING THE PRODUCT OF ONE CYCLE AS TEMPLATE IN THE NEXT IS TO LOOK AT WHAT HE MADE WITH NEAREST NEIGHBOR.

A. THAT'S CORRECT.

Q. AND HE DIDN'T DO THAT.

A. I'VE SAID ALREADY MANY TIMES HE DIDN'T DO THAT.

Q. NOW, THE NEXT EXPERIMENT HE DID IS AN EXPERIMENT YOU DIDN'T TALK ABOUT, AND THAT'S EXPERIMENT NUMBER 10.

AND YOU'RE FAMILIAR WITH THAT, OF COURSE.

A. WELL, I HAVE TO LOOK AT IT AND SEE WHAT IT IS.

(PAUSE IN PROCEEDINGS)

THE WITNESS: YES.

Q. (BY MR. PASAHOW) HE'S USING HIS -- HIS SAME DNA-II TEMPLATE.

A. YES.

Q. AND HE'S USING HIS SAME TWO PRIMERS.

A. IN THIS CASE, HE STARTS OUT WITH THE DUPLEX.

Q. I'M SORRY. HE DOESN'T -- HE DOESN'T HAVE ANY PRIMERS.

A. EXACTLY.

Q. SO THIS IS JUST DNA-II WITH THE TWO END C'S MISSING.
A. THAT'S RIGHT.

Q. BUT THE SAME DNA-II --

A. YES.

Q. -- TEMPLATE.

A. YES.

Q. AND HE'S USING THE SAME RADIOACTIVE -- I'M SORRY.

HE'S USING THE SAME NON-RADIOACTIVE BASES FOR THE A'S, G'S AND T'S; IS THAT RIGHT?

A. THAT'S WHAT I'M ASSUMING, YES.

Q. BUT THERE'S SOMETHING SPECIAL ABOUT THE C'S IN THIS EXPERIMENT.

A. YES.

Q. AND WHAT IS THAT?

A. WELL, I CANNOT SAY FOR SURE, BUT HE INDICATES HERE THAT HE USES CTP, WHICH IS A RIBOTRIPHOSPHATE NOT A DEOXYTRIPHOSPHATE, AND HE PUTS DOWN, LOOK, THERE'S SOMETHING UNUSUAL ABOUT THIS.

Q. (INDICATING.)

A. YES, THAT'S CORRECT.

Q. SO THAT'S HOW HE WOULD INDICATE THE RNA?

A. THAT'S HOW WE NORMALLY DO THIS, YES.

Q. NOW, DR. KORNBERG TOLD US THAT YOU CAN'T INCORPORATE THE RNA BASES WITH HIS ENZYME IF YOU USE MAGNESIUM; THAT YOU'VE GOT TO USE MANGANESE.

A. YOU HAVE TO USE MANGANESE, RIGHT.

Q. AND WHAT WAS DR. KLEFFE USING?
Q. AND, IN ESSENCE, THIS WAS A CONTROL OF SOME KIND?
A. YES.
Q. AND IT CAME OUT WRONG.
A. YES.
Q. NOW, IS IT CORRECT THAT, AFTER DR. KLEPPÉ DID THIS EXPERTMENT, HE STOPPED USING THE C14 RADIOACTIVELY-LABELLED BASES?
A. HE HAD SOME DIFFICULTY WITH THE C14, YES, WITH THE PURITY OF THEM.
Q. AND HE WENT TO USING P32 BASES AFTER HE DID THIS CONTROL.
A. HE DID SOME EXPERIMENTS WITH P32, YES.
(PAUSE IN PROCEEDINGS)
Q. (BY MR. PASAHOW) NOW, THE OTHER EXPERIMENT YOU TALKED ABOUT WAS 28, AND I'D LIKE TO TALK TO YOU ABOUT SOME OF THE THINGS YOU SAID THERE.
(PAUSE IN PROCEEDINGS)
Q. (BY MR. PASAHOW) LET ME BEGIN WITH THE FIRST PAGE OF EXPERIMENT 28, WHICH IS MARKED B-217A.
NOW, YOU WERE TELLING ME THAT HE DID EXPERIMENT 28 IN MARCH. I DON'T SEE A DATE ON THIS PAGE. DID YOU FIND ONE?
A. NO, BUT I'M JUST LOOKING AT THE SEQUENCE. I THINK I CAN SEE THE MONTH THREE IN THERE. I CAN'T SEE THE EXACT DATE.
Q. AND THAT'S --
A. IT'S A THREE SLASH, AND THEN I THINK THAT'S WHERE THE PUNCH
HOLE WAS IN THE COPY.

Q. NOW, IN THIS EXPERIMENT, DR. KLEPPE AGAIN BEGINS BY ADDING
SOME WATER. HERE, HE'S ADDING 10 . . . IS THAT MICROLITERS OF
WATER?

A. YES, YES.

Q. AND WHY WOULD HE BE ADDING WATER?

A. TO, AGAIN, BRING THE REACTION UP TO THE CONCENTRATION HE
WANTED. IT'S THE NORMAL WAY ONE SETS UP A PROTOCOL.

Q. NOW, YOU SAID THAT IN THIS PART THREE HERE, THERE'S NO
INDICATION THAT DR. KLEPPE ADDS ANY POLYMERASE.

A. THAT'S CORRECT.

Q. AND YET YOU'RE ASSUMING HE ADDED POLYMERASE.

A. VERY MUCH SO.

Q. NOW, WE SAW ANOTHER ONE OF HIS NOTEBOOKS WHERE HE HAD GONE
BACK AFTER THE CARBON WAS REMOVED, HE'D WRITTEN IN IN INK THAT
THE POLYMERASE WAS INVOLVED IN THE EXPERIMENT.

A. YES.

Q. DO YOU RECALL THAT?

A. YES, I DO.

Q. NOW, OF COURSE, HERE, DR. KLEPPE NEVER WENT BACK AND SAID HE
USED POLYMERASE.

A. HE DID NOT MAKE THE CORRECTION, YES.

Q. BUT YOU'RE ASSUMING HE USED POLYMERASE AT THAT STEP.

A. OH, YES, VERY MUCH SO.
Q. AND, OF COURSE, IF YOU ASSUME HE DID WHAT HE WROTE DOWN
RATHER THAN THAT HE ADDED POLYMERASE, WHAT WE’VE GOT IS AN
EXPERIMENT WITH A FAILED CONTROL.

A. NOTHING COULD HAPPEN, YES. THERE WOULD NOT BE ANY ENZYME
THERE.

Q. SO WHAT YOU’VE DONE IS, YOU’VE ASSUMED THAT POLYMERASE IS
THERE BECAUSE THAT MAKES THE EXPERIMENT LOOK LIKE THE REACTION
THAT YOU HAVE IN MIND.

A. (SHAKING HEAD.) NO. I JUST -- WHAT I’VE DONE IS GONE BACK
TO MY RECOLLECTION.

I KNOW HOW DR. KLEPPE WORKED, WHAT HE KNEW ABOUT THE
POLYMERASE, AND I WOULD NOT DO THE EXPERIMENT -- AND ESPECIALLY
HE WOULDN’T DO THE EXPERIMENT WITHOUT ADDING ENZYME.

Q. WELL, HE DID CONTROLS WHERE HE PUT EVERYTHING IN AND LEFT
OUT ENZYME; DID HE NOT?

A. YES, BUT THIS IS A SERIES. THIS IS A SEQUENTIAL SERIES, SO
YOU CANNOT DO IT THAT WAY.

Q. I SEE. SO HE WOULDN’T RUN A CONTROL AS PART OF HIS SERIES?

A. NO. HE WOULD RUN A CONTROL AS A SEPARATE EXPERIMENT.

Q. WELL, YOU TOLD US --

A. NOT AS A PART OF A SEQUENTIAL SERIES IN THIS CASE. IT’S THE
SAME REACTION HE’S CARRYING OUT. YOU CANNOT SWITCH A REACTION
IN MID-STREAM.

Q. YOU TOLD US, SIR, THAT IN EXPERIMENT NINE, RIGHT IN THE
MIDDLE OF THINGS, HE RAN A CONTROL AT THE FIRST PART OF 9-A.

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A. YES, BUT HE DIDN'T PUT IN ENZYME IN THAT PARTICULAR ONE.

Q. THAT'S RIGHT.

A. HE JUST CONTINUED. IN OTHER WORDS, HE DID NOT DO AREACTION WHICH MADE NO SENSE.

Q. THERE, WHAT HE DID IS, HE DIDN'T HEAT IT UP.

A. EXACTLY. BECAUSE IN THAT PARTICULAR CASE, HE HAD FROZEN THE REACTION, SO THIS WAS A CHECK ON THE REACTION AT THAT PARTICULAR TIME.

Q. SO HERE, IN ORDER TO GET THIS TO MAKE SENSE AS A REACTION, YOU SAY HE ADDED POLYMERASE.

A. YES.

Q. OKAY. WELL, LET'S PUT THAT IN.

HE CALLS THAT DNA-P?

A. DNA-P. VERY GOOD.

Q. AND WHERE WOULD THAT GO? SOMEWHERE IN HERE (INDICATING)?

A. YES, AT THE END.

Q. NOW, YOU DID SOME CALCULATIONS WHERE YOU HAD TO WORRY ABOUT THE VOLUME OF THE DIFFERENT --

A. YES.

Q. -- FLUIDS?

A. YEAH.

Q. HOW MUCH FLUID DID YOU ASSUME THE DNA POLYMERASE WAS?

A. ACTUALLY, IN THAT PARTICULAR CASE, I DID NOT ADD THE VOLUME FOR THE DNA POLYMERASE AT ALL, BECAUSE I KNEW YOU WERE GOING TO ASK ME THAT QUESTION, SO I WANTED TO BE AS CONSERVATIVE AS I CAN.

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BE IN MY CALCULATIONS.

Q. SO YOU ASSUME HE ADDED DNA POLYMERASE WITHOUT ADDING ANY LIQUID.

A. I DIDN'T ADD A LIQUID BECAUSE THAT WOULD ONLY GET THE NUMBERS HIGHER.

Q. WELL, IT'S TRUE, ISN'T IT, THAT TO ADD DNA POLYMERASE, YOU HAVE TO ADD LIQUID.

A. I'LL BE HAPPY TO TAKE A TABLE AND WRITE IN "ADD ONE DNA POLYMERASE" AND CORRECT THE REACTION.

Q. THE QUESTION IS, SIR: TO ADD DNA POLYMERASE, YOU HAVE TO ADD LIQUIDS.

A. OF COURSE, YOU HAVE TO ADD LIQUIDS.

Q. NOW, ON THIS NEXT PAGE, DID YOU -- DID YOU CHANGE ANYTHING THAT DR. KLEPPE WROTE DOWN IN YOUR ASSUMPTIONS ON THIS PAGE?

A. NO. WHAT I SAID WHEN I TALKED ABOUT THIS ON DIRECT, I SAID DR. KLEPPE DID NOT INDICATE THAT HIS SPECIFIC ACTIVITY OF THE ALPHADEOXY CTP WAS THE SAME AS IN THE BEGINNING OF THE EXPERIMENT.

Q. DOES THAT MEAN THAT HE LEFT SOMETHING OUT THAT --

A. YES.

Q. -- YOU THINK HE PUT IN?

A. WELL, THERE'S ONE OF TWO WAYS THIS COULD HAVE BEEN DONE: HE EITHER DID NOT WRITE DOWN THAT THERE WAS THE SAME AMOUNT OF COLD CTP THERE, OR THE OTHER POSSIBILITY IS THAT HE MADE UP A COCKTAIL WITH A RADIOACTIVE CTP WHICH ALREADY HAD THE COLD CTP.
Q. LET'S GO BACK TO THE FIRST PAGE HERE, 217A, AND, DOCTOR, THE RADIOACTIVE BASE THIS TIME IS C?
A. IS ALPHA C, YES.
Q. AND HE SAYS HERE THAT HE ADDS C TWICE. HE SAYS HE ADDS A MICROLITER OF DCTP HERE, AND HE SAYS HE ADDS 20 MICROLITERS OF DCTP HERE.
A. THAT'S CORRECT.
Q. WHY IS HE ADDING DCTP TWICE?
A. TO MAKE UP THE SPECIFIC ACTIVITY WHICH HE WANTED IN HIS EXPERIMENTS.
Q. SO HERE HE WRITES BOTH DOWN SPECIFICALLY.
A. YES, THAT'S CORRECT.
(PAUSE IN PROCEEDINGS)
Q. (BY MR. PASAHOW) NOW, IN DNA-IV, HE ADDS SOME MORE RADIOACTIVE DCTP?
A. CORRECT.
Q. AND HE DOES NOT WRITE DOWN THAT HE ADDS ANY DCTP THAT'S NOT RADIOACTIVE.
A. YEAH. AS I SAID IN MY DIRECT, THE RULE IN DR. KHOＲANＡ'S LABORATORY WAS THAT YOU WOULD MAINTAIN THE SAME SPECIFIC ACTIVITY DURING THE EXPERIMENT. YOU CANNOT CHANGE THE SPECIFIC ACTIVITY BECAUSE YOU CANNOT REALLY CONCLUDE ANYTHING FROM THE EXPERIMENT.
Q. THE QUESTION, SIR, IS: WHEN DR. KLEPPE --
A. UH-HUH.

Q. -- WROTE DOWN WHAT HE PUT IN, HE DID NOT WRITE DOWN THAT HE PUT IN ANY COLD DCTP IN STEP FOUR.

A. WELL, HE WOULD HAVE TRANPOSED HIS -- AS I MENTIONED, THE PROCEDURE THAT HE USED, WHEN HE TRANSPOSES EXPERIMENTS FROM HIS NOTE PAD INTO THE BOOK, HE DID NOT PUT IT DOWN, THAT’S CORRECT.

Q. NOW, YOU DIDN’T SEE HIM DO THIS EXPERIMENT.

A. I DID NOT SIT OVER HIS SHOULDER, NO.

Q. AND YOU DON’T KNOW WHETHER HE ADDED COLD DCTP AS YOU SAW.

A. NO, I DIDN’T SEE IT.

Q. SO WHAT YOU’RE ASSUMING IS, HE DID ADD COLD DCTP.

A. YES.

Q. NOW, IS THAT SOMETHING YOU ASSUMED IN ORDER TO HELP THE CETUS ASSUMPTIONS ABOUT THIS EXPERIMENT?

A. NO. THAT’S SOMETHING THAT I KNOW FROM MY RECOLLECTION THE WAY DR. KLEPPE CARRIED OUT HIS EXPERIMENTS, AND, AS I SAID BEFORE, TAKING INTO ACCOUNT THE PROCEDURES THAT WE USED IN THE KHORANA LABORATORY.

Q. WHAT IF YOU ASSUME THAT DR. KLEPPE WAS THE CAREFUL NOTE-TAKER THAT HIS WIFE TOLD US HE WAS. HOW WOULD THAT AFFECT THE CALCULATIONS YOU MADE?

A. LET’S SAY HE ADDED ONE MICROLITER TO THIS, AND IT WOULD NOT HAVE -- ALL IT WOULD HAVE DONE IS INCREASE THE VOLUME AND THE SAMPLES WOULD HAVE BEEN MORE DILUTED.

(PAUSE IN PROCEEDINGS)
Q. (By Mr. Pasahow) He would have added one microliter of what?
A. Of, let's say, deoxy CTP, which he did not put down on the notes there.

Q. Well, what if we assume, instead of what you're saying, that Dr. Kleppe was, as we've been told, a very careful note-taker and he did write down what he put in? How would that affect those graphs that you showed us?
A. That would . . . affect the second part of the graph. It would not affect cycle two and three. It would affect the subsequent ones, because the specific activity would change.

And it's -- it's like doing an experiment and using one ruler and, in the middle of the experiment, changing the ruler, which is not the way the experiments were done in Dr. Khorana's laboratory.

Q. What it would do is, it would reduce enormously the amounts that you found from your calculations in steps four, five and six.
A. That's correct.

Q. So you say here, we have to add cold DCTP.
A. Yes.

Q. And how much fluid in your calculations did you assume that was put in?
A. I didn't put it in the calculations.
(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, THE LAST PAGE OF THIS EXPERIMENT
WE’VE MARKED IS A POSTER B-217C.

AND ON THIS PAGE, DO YOU THINK DR. KLEPPE WROTE DOWN
WHAT IT IS YOU NOW_ASSUME HE DID?

A. NO. AS I TOLD ON MY DIRECT, IN EXPERIMENT NUMBER SIX, HE
DID NOT PUT IN THAT HE WAS TAKING THE REACTION AND PUTTING IT
THROUGH A HEAT CYCLE.

Q. NOW, YOU’VE TOLD US IN EXPERIMENT NINE, IN THE MIDST OF
THINGS, HE DID A NO-HEAT CYCLE.

A. THAT’S RIGHT.

Q. AND HERE WHERE HE SAYS HE DID NOT HEAT, YOU_ASSUME HE DID
HEAT.

A. YES, BECAUSE IN SEVERAL OF HIS EXPERIMENTS, WAS TO TEST THE
EFFECT OF HEAT CYCLES. THAT’S WHAT THE EXPERIMENT WAS ALL
ABOUT.

Q. WELL, IT WOULD -- IT WOULD BE A REASONABLE THING, TO DO A
CONTROL IN THE MIDST -- AT THE END OF THIS EXPERIMENT; WOULD IT
NOT?

A. (SHAKING HEAD.) ALL IT WOULD HAVE MEANT, HE DID ONLY FOUR
CYCLES INSTEAD OF FIVE.

Q. SIR, THE QUESTION WAS: WOULD IT BE A REASONABLE THING TO DO
A CONTROL AT THE END OF THIS EXPERIMENT?

A. I DON’T THINK SO, NO.

Q. YOU DON’T THINK IT WOULD BE REASONABLE --
A. No.

Q. -- to do a control.

A. No, not in the way the experiments were set up.

Q. So, somewhere in here, you want me to write that he heated it?

A. Yes.

Q. Where would that go?

A. Just where you pointed at.

Q. Right here?

A. Just after -- before, of course, he added the enzyme.

It was after he diluted 60 microliters, and then I would say -- I think there is a good place.

(Pause in proceedings)

Q. (By Mr. Pasahow) Of course, he told us the temperature here was 15 degrees centigrade.

A. He carried out the reaction the same way as before, yes.

Q. But he doesn't tell us up here heated to 110 degrees or --

A. No.

Q. How hot do you think he heated it?

A. I would -- I would expect he would have heated it normal 100 degrees. He made a point in experiment 5-B to indicate this was 110 because he put a paraffin on it as well.

Q. Well, he made a point in 5-A to tell us it was a hundred.

A. A hundred, that's right. And he did not put it in in number six.
Q. HE DIDN'T PUT IN ANYTHING ABOUT THIS.
A. NO.

Q. NOW, OTHER THAN THOSE CHANGES, DO YOU THINK DR. KLEPPE WROTE DOWN WHAT HE -- WHAT HE DID?
A. I THINK THE MOST EFFECT, YES, I THINK SO. I THINK THERE MIGHT HAVE BEEN ONE REACTION SOMEWHERE WHERE HE DIDN'T PUT DOWN "CHILL," IF WE WANTED TO BE SPECIFIC ABOUT IT.

Q. IN EXPERIMENT SIX, YOU SAY HE TOOK PART OF WHAT WAS IN FIVE --
A. YES.

Q. -- AND DID SOMETHING TO IT?
A. RIGHT.

Q. NOW, HERE IN 5-A, HE SAYS WHAT HERE ABOUT 24? HE'S DOING SOMETHING? WHAT DOES THAT SAY?
A. I CAN'T READ IT FROM HERE.

Q. DO YOU HAVE YOUR -- YOUR COPY OF THAT?
A. I DON'T THINK SO.

(PAUSE IN PROCEEDINGS)

THE WITNESS: I THINK THAT'S FROM . . . PAGE 49. IT SAYS "CONTENTS OF 28 4-A TRANSFERRED."

Q. (BY MR. PASAHOW) SO THAT WOULD BE THE END OF EXPERIMENT 28(4-A), HE TAKES THAT AND TRANSFERS IT?
A. UH-HUH, YES.

Q. NOW, HERE HE SAYS, "28(4-B) HEATED TO 110 DEGREES"?
A. YES.
Q. AND THAT MEANS HE TOOK WHATEVER HE GOT FROM 28(4-B) AND HE DID SOMETHING TO IT.
A. YES, YES.
Q. AND HERE IN SIX, HE SAYS, "28(6) DILUTED TO 60 MICROLITERS"?
A. YES.
Q. ARE YOU ASSUMING THAT HE TOOK SOME FLUID THAT HE GENERATED IN STEP SIX HERE?
A. NO. HE WOULD HAVE TAKEN 28(5), BECAUSE THAT WAS THE -- OBVIOUSLY, THE REACTION THAT HE STARTED WITH, THAT HE FINISHED WITH.
Q. SO THIS IS ANOTHER THING --
A. YES.
Q. -- WHERE YOU THINK HE WROTE SOMETHING DOWN --
A. RIGHT.
Q. -- THAT WAS DIFFERENT THAN HE DID?
YES?
A. HE TOOK THAT MIXTURE AND THEN DILUTED TO 60 MICROLITERS.
Q. DID HE TAKE 25-A OR 25-B?
A. HE TOOK -- IN THIS PARTICULAR CASE . . . HE DOESN'T INDICATE WHICH ONE HE TOOK.
Q. WHICH DID YOU ASSUME HE TOOK?
A. 25-A.
Q. WHY?
A. BECAUSE THAT'S THE LOGICAL WAY THAT I WAS FOLLOWING THROUGH THE EXPERIMENTS. BUT IT DOESN'T MAKE MUCH DIFFERENCE WHETHER HE
TOOK A OR B, BECAUSE THE VOLUMES ARE GOING TO BE VERY MUCH THE
SAME, AND ALSO THE AMOUNT OF RADIOACTIVITY GOING IN IS VERY MUCH
THE SAME.

Q. COULD HE HAVE TAKEN 25-A AND B TOGETHER?
A. HE COULD HAVE DONE THAT, TOO, YES.

Q. NOW, IF HE TOOK 25-A AND B TOGETHER, THAT WOULD HAVE A
RATHER DRAMATIC IMPACT ON YOUR CALCULATION; IS THAT RIGHT?
A. THAT’S RIGHT. THAT’S -- THE LAST CYCLE WOULD NOT BE
ACCURATE UNDER MY CALCULATIONS, THAT’S CORRECT.

Q. SO WHERE HE SAYS 28(6) HERE, YOU THINK THAT HE REALLY DID --
AT LEAST, IN YOUR CALCULATION, YOU ASSUME HE DID 28(5-A).
A. YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, WHEN YOU WERE CALCULATING THROUGH
THIS, YOU TOLD US YOU USED SOMETHING CALLED NORMAL COUNTS OR
NORMALIZED COUNTS?
A. NORMALIZED COUNTS, YES.

Q. NOW, WHERE IN THE NOTEBOOK DID YOU FIND NORMALIZED COUNTS?
A. WELL, AS I SAID, IN THE NOTEBOOK, IT SHOWS WHAT WE CALL THE
RAW COUNTS, THE COUNTS AS THEY COME OFF FROM THE SCINTILLATION
COUNTER.

Q. SO YOU WORKED WITH THE PEOPLE FROM DU PONT TO MAKE SOME
CALCULATIONS THAT ARE SHOWN IN THAT GRAPH?
A. NO. NO, I DIDN’T WORK WITH THE PEOPLE. I CALCULATED THOSE
MYSELF.
Q.  WHO -- DID YOU DO THE GRAPHS?

A.  YES.  I MADE THE GRAPHS AND THEY WERE RE-DRAWN.  THE
ORIGINAL GRAPHS I DID, YES.

Q.  AND HOW -- HOW DID YOU GO ABOUT DOING THESE NORMALIZED
COUNTS?

A.  BY ADJUSTING FOR THE VOLUME CHANGES, AS I INDICATED IN MY
DIRECT EXAMINATION.

Q.  WELL, FOR EXAMPLE, WE FOUND THAT WHEN DR. KHORANA AND DR.
KLEPPE PUBLISHED THEIR DATA, THEY TAKE THE ZERO TIME PERIOD
RADIOACTIVITY THAT THEY STARTED WITH AND THEY ZERO THAT OUT.

A.  UH-HUH.

Q.  SO THEY START AT THE BASELINE.

A.  UH-HUH.

Q.  DID YOU DO WHAT THEY DID WHEN THEY PUBLISHED DATA?  DID YOU
TAKE THAT OUT AND ZERO IT?

A.  I STARTED OUT WITH A REACTION TWO, WHICH WAS REALLY THE
FIRST CYCLE, AND SUBTRACTED THE -- THE COUNTS FROM REACTION ONE
FROM THEM.  SO I ZEROED THEM OUT THAT WAY.

I ACTUALLY SHOWED ON MY GRAPH THAT THERE WERE SOME
COUNTS TO START WITH.  YOU LOOK AT THE GRAPH, IT'S SLIGHTLY
HIGHER FROM THE AXIS, BECAUSE I WANTED TO INDICATE THAT THERE
WERE COUNTS ALREADY THERE.

Q.  SO WHERE THE -- WHEN DR. KHORANA AND DR. KLEPPE PUBLISHED
THEIR DATA, THEY'D START OUT AT ZERO; YOU STARTED OUT SOMEWHERE
ABOVE THE ZERO LINE.
A. YES.

Q. WAS THAT THE LABORATORY GENERAL POLICY, TO LEAVE THE ZERO IN?

A. NO. I JUST WANTED TO MAKE SURE THAT I WAS SHOWING THAT THERE WERE COUNTS IN THERE, BECAUSE I KNEW YOU WERE GOING TO ASK ME ABOUT IT, SO I THOUGHT I'D BETTER SHOW THERE WERE COUNTS IN THERE.

Q. SO THE EFFECT OF THAT WAS TO MOVE THE GRAPHS UP.

A. IT MAKES NO DIFFERENCE IN THE EXPONENTIAL ASPECT OF THE GRAPH.

Q. IT MADE FOR LARGER NUMBERS.

A. LARGER NUMBERS, BUT, STILL, THE LINES WOULD BE PARALLEL.

Q. NOW, ONE OTHER THING ABOUT EXPERIMENT SIX: HOW MANY HOURS DID IT GO ON?

A. A LOT OF TIME. YOU CAN ADD UP THE TOTAL AMOUNT OF TIME.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) IN STEP ONE, IT WENT ON FOR . . .

A. FOR TWO HOURS.

Q. TWO HOURS?

A. YES.

Q. AND IN STEP TWO, IT WENT ON FOR . . .

A. THREE HOURS.

Q. THREE HOURS.

A. THAT'S FIVE HOURS.

Q. AND IN STEP THREE, IT WENT ON FOR . . .
A. I can't read that from here, whether it's two hours or three hours.

Q. Why don't you look at your copy? I believe it's three hours.

A. Yes.

(PAUSE IN PROCEEDINGS)

THE WITNESS: Yeah, I think it's three hours. So that would be eight hours.

Q. (by Mr. Pasahow) Then on step four, it went on . . .

A. Two hours.

Q. Two hours.

A. Yes. That would be 10.

Q. And in step five, it went on for . . .

A. Two hours. That would be 12.

Q. And then in this last round, step six, it went on for two more hours?

A. That's right.

Q. And so there was DNA polymerase sitting in there for 14 hours?

A. There were new additions of DNA polymerase made during the experiments, yes.

Q. Now, you're familiar with the phenomena Dr. Kornberg described for us called De Novo synthesis?

A. Very much so.

Q. And, in fact, it was something that was discussed there in
THE LABORATORY; IS THAT RIGHT?
A. YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) LET ME SHOW YOU AN EXHIBIT THAT WAS MARKED AS EXHIBIT A-68.
A. YES.

Q. ARE YOU FAMILIAR WITH THAT?
A. YES, I AM.

Q. WHAT IS IT?
A. IT'S ANOTHER SEMINAR PRESENTATION BY DR. KJELL KLEPPE.

MR. PASAHOW: YOUR HONOR, I'D OFFER EXHIBIT A-68.

THE COURT: ANY OBJECTION?

MR. FIGG: NO OBJECTION, YOUR HONOR.

THE COURT: A-68 IS ADMITTED.

THE CLERK: A-68 INTO EVIDENCE.

(PLAINTIFF'S EXHIBIT A-68 RECEIVED IN EVIDENCE)

Q. (BY MR. PASAHOW) NOW, EXHIBIT A-68 STARTS OUT AT THE TOP WITH A DRAWING OF THE SEQUENCE OF DNA-II.
A. DNA-II, THAT'S CORRECT.

Q. SO APPARENTLY DR. KLEPPE ON THIS DAY WAS TALKING ABOUT DNA-II.
A. PART OF HIS EXPERIMENTS RELATE TO DNA-II, YES.

Q. AND HE THEN GOES ON AND HE HAS A GRAPH HERE. AND WHAT'S THAT A GRAPH OF?
A. THAT'S A GRAPH WHICH HAS NOTHING TO DO WITH DNA-II. THAT'S A GRAPH WHICH HAS TO DO WITH ALTERNATING A-T SYNTHESIS.

Q. IT'S A GRAPH OF DE NOVO SYNTHESIS; ISN'T IT?

A. NOT NECESSARILY. I THINK, LOOKING AT THE NOTEBOOKS CORRELATING THIS EXPERIMENT WITH THE GRAPH, I THINK HE DID PUT SOME ALTERNATING A-T IN THOSE EXPERIMENTS, SO THAT'S NOT EXACTLY DE NOVO.

"DE NOVO" MEANS THERE'S NOTHING TO START WITH.

Q. SO THIS WOULD BE ONE WHERE HE PUT IN VERY SHORT SEGMENTS OF A-T TO BEGIN WITH?

A. NO, NO. THEY ACTUALLY WOULD BE A POLYMER, POLYNUCLEOTIDE. ALTERNATING A-T IS A POLYMER WHICH SYNTHESIZES VERY IRREGULARLY AND ACTUALLY MAKES VERY LONGER DNA.

Q. NOW, DR. KORNBERG TOLD US THAT DE NOVO SYNTHESIS CAN OCCUR JUST BY THE CONTAMINATION OF THE DNA POLYMERASE?

A. I THINK, DEPENDING ON THE PREPARATION OF THE DNA POLYMERASE, IF YOU LET THE DNA POLYMERASE SIT FOR A VERY LONG PERIOD, THERE'S A SLACK PERIOD WHERE NOTHING ELSE HAPPENS, IF YOU HAVE NOTHING ELSE THERE, JUST THE TRIPHOSPHATES, AND AFTER A VERY LENGTHY TIME, YOU START SEEING SOME SYNTHESIS. THIS IS USING THE SAME BATCH OF ENZYME FOR THIS VERY LENGTHY TIME.

Q. THE QUESTION, SIR, WAS: DR. KORNBERG, YOU'LL RECALL, TOLD US THAT DE NOVO SYNTHESIS CAN OCCUR EVEN THOUGH YOU DON'T ADD ANY DNA OTHER THAN THE CONTAMINATION IN THE POLYMERASE.

A. THAT'S WHAT I JUST EXPLAINED TO YOU, YES.
Q. AND IT HAPPENS IF THE DNA POLYMERASE, AS YOU SAY, IS LEFT IN
THE EXPERIMENT OVER A PERIOD OF TIME.
A. THAT'S CORRECT.
Q. AND THE REASON IT OCCURS IS, APPARENTLY, THESE CONTAMINATING
PIECES START FORMING DUPLEXES WITH EACH OTHER.
A. YES. IT IS THOUGHT THAT ACTUALLY THOSE SEGMENTS OF
ALTERNATING A-T ARE BOUND TO THE ENZYME WHEN YOU PURIFY THE
ENZYME.
Q. AND DR. KORNBERG TOLD US YOU COULD ALSO SET SEGMENTS OF G-C.
DO YOU RECALL THAT?
A. YES. A LITTLE BIT MORE DIFFICULT. A LOT MORE DIFFICULT,
ACTUALLY.
Q. AND, OF COURSE, IF YOU -- IF YOU HAD A SOLUTION IN WHICH YOU
WERE MEASURING RADIOACTIVE C'S --
A. UH-HUH.
Q. -- AND YOU HAD DE NOVO SYNTHESIS OF THESE G-C CHAINS, WHAT
YOU'D GET IS THE SAME KIND OF RESULTS AS YOU GET IF YOU
INCORPORATE THE C'S WITH A PRIMER.
A. YOU WOULD -- YOU WOULD SEE INCORPORATION OF C, RIGHT.
Q. AND YOU'D SEE EXPONENTIAL INCORPORATION; IS THAT RIGHT?
A. IF THE REACTION WOULD GO AND START. BUT I SHOULD ALSO
INDICATE THAT THE REACTION WITH C-G, THE DE NOVO SYNTHESIS, IS
EXTREMELY POOR. IT'S NOT A REACTION WHICH OCCURS READILY.
Q. UH-HUH.
A. A-T OCCURS QUICKER THAN G-C.
Q. WELL, WE DON'T KNOW IF A-T WAS HAPPENING WITH -- UNLESS
YOU'VE GOT A LABEL OF AN A OR A T; IS THAT CORRECT?
A. THAT'S CORRECT.
Q. NOW, THERE'S A . . . YOU TOLD US THAT, WITH EXPERIMENT 28,
THERE WAS NO ANALYSIS OF THE PRODUCT.
A. THAT'S RIGHT.
Q. NOW, THIS TIME, DR. KLEPPE USED THE P32-LABELED C'S.
A. UH-HUH.
Q. SO HE COULD HAVE DONE A NEAREST NEIGHBOR ANALYSIS.
A. I THINK IF HE WOULD HAVE HAD A LOT OF MATERIAL LEFT AT THE
END, YES, HE COULD HAVE.
Q. AND IF HE HAD, WE'D KNOW WHETHER HE WAS GETTING DE NOVO
SYNTHESIS, FOR EXAMPLE, OR THE PRODUCT HE INTENDED.
A. WHEN ONLY DE NOVO SYNTHESIS COULD BE THE G-C, NOT THE A-T,
THAT WOULD HAVE SHOWN IN THE A-T OBVIOUSLY, RIGHT. BUT, YOU
KNOW, ALL OF THE EXPERIMENTS WHICH HE HAD CARRIED OUT WITH THE
REPAIR HAD NEVER INDICATED ANY EVIDENCE OF DE NOVO G-C SYNTHESIS
IN THOSE CONDITIONS.
Q. NOW, JUST BELOW HIS CHART OF THIS ALTERNATING SEQUENCES
HERE, WHETHER IT'S DE NOVO SYNTHESIS OR SOMETHING ELSE, DR.
KLEPPE HAS A REFERENCE HERE TO DNA-II?
A. AND DNA-I.
Q. YES. AND AS TO DNA-II, HE'S TALKING ABOUT THE KIND OF
INCORPORATION HE'S GETTING OF THESE RADIOACTIVE C'S --
A. YES.
Q. -- IS THAT RIGHT?
A. YES, HE IS.
Q. AND HE SAYS .5 OF THESE ARE INCORPORATED?
A. YES.
Q. AND THAT WOULD BE .5 PER MOLECULE OF TEMPLATE, I ASSUME.
A. YES.
Q. AND THEN HE SAYS, "SHOULD BE EXPECTED TWO."
A. RIGHT. YOU KNOW, WE TALKED ABOUT THAT SEVERAL TIMES. HE
SHOULD GET TWO C'S AT THE TWO ENDS OF DUPLEX II.
Q. SO HE'S INDICATING DURING THIS THAT THE -- THE TWO C'S WOULD
BE HERE AND HERE?
A. YES, RIGHT AT THE TERMINANT, RIGHT.
Q. WHAT HE TOLD THE GROUP DURING THIS LECTURE WAS THAT HE
WASN'T GETTING THE KIND OF INCORPORATION THAT HE THOUGHT HE
SHOULD GET.
A. YES, BECAUSE HE INDICATES HE SHOULD EXPECT TWO, WHICH HE
INDICATES IN THE NOTES.
I'VE GONE BACK AND LOOKED AT THAT EXPERIMENT, ACTUALLY,
AND THE TRIPHOSPHATE CONCENTRATION THAT HE WAS USING DURING THAT
EXPERIMENT WAS CONSIDERABLY LESS THAN THE TRIPHOSPHATE
CONCENTRATION THAT HE USED IN EXPERIMENT NUMBER 28.
Q. NOW, DID YOU ALSO LOOK FOR OTHER EXPERIMENTS WHERE DR.
KLEPPPE USED THE DNA-II TEMPLATE AND THE NINE-BASE PRIMER AND THE
10-BASE PRIMER WHERE HE MIGHT HAVE DONE A NEAREST NEIGHBOR
ANALYSIS?
Q. I think you added something in your answer that I didn't ask, and that is, did you look for an experiment with doctor -- where Dr. Kleppe used the same template and the same primers and he did a nearest neighbor analysis to look at the product?

A. He did some with the T4 DNA polymerase.

Q. And that was experiment 48.

A. I think that was 48, yes.

Q. And you -- let's take a look at experiment 48. I've got a poster here beginning with B-224.

(Pause in proceedings)

Q. (By Mr. Pasahow) And this begins by saying 5/30?

A. This would be the 30th of May, I guess, yes.

Q. 1969.

A. 1969, yes.

Q. So it's, of course, after experiment 28.

A. Right.

Q. Now, in this experiment 48, Dr. Kleppe again is using the radioactively-labeled C's?

A. Yes, he is.

Q. Now, here again, he only lists it once. He doesn't say he's adding hot and cold.

A. Right.

Q. Do you assume he added cold even though he doesn't list it?

A. What he would have done is made up the CTP to the specific
ACTIVITY THAT HE DESIRED IN HIS EXPERIMENT, WHICH WOULD MEAN, YOU KNOW, MAKING OF THE RADIOACTIVE PLUS IN SOME CASES SOME COLD, DEOXY CTP.

Q. SO HERE WE CAN ASSUME HE WROTE DOWN WHAT HE REALLY PUT IN.
A. IN THIS CASE, HE MIGHT HAVE DILUTED IT THE SAME WAY AS HE COULD HAVE DILUTED THE ONE IN EXPERIMENT 28.

Q. THE QUESTION WAS, HERE WE'RE ASSUMING HE WROTE DOWN WHAT HE PUT IN?
A. HE INDICATES THE CONCENTRATION OF THE DEOXY CTP IN THIS CASE, YES.

Q. AND HE SAYS THAT HE PUT IN POLYMERASE HERE.
A. YES.

Q. SO WE DON'T HAVE TO ASSUME HE PUT THAT IN.
A. NO.

Q. HE WROTE IT DOWN.
A. HE INDICATES IT'S A T4 POLYMERASE, YES.

Q. AND HE TELLS US THAT HE HEATED IT HERE.
A. YES.

Q. SO I GUESS WE DON'T HAVE TO ASSUME HE HEATED IT.
AND HE -- HE'S USING THE SAME DNA-II TEMPLATE; IS THAT RIGHT?
A. IT SAYS THERE DUPLEX II. IT SAYS NONA, AND IT STATES A DECA, YES.

Q. SO THIS IS THE SAME DNA --
A. RIGHT.
Q. -- TEMPLATE --

A. YES.

Q. -- THAT HE USED IN EXPERIMENT 28.

A. RIGHT.

Q. AND IT'S THE SAME DNA TEMPLATE HE USED IN EXPERIMENT NINE.

A. YEAH.

Q. AND IT'S THE SAME PRIMERS --

A. YES.

Q. -- HE USED IN EXPERIMENT 28.

A. CORRECT.

Q. AND IT'S THE SAME PRIMERS HE USED IN EXPERIMENT NINE.

A. CORRECT.

Q. NOW, THIS TIME, DR. KLEPPE DOES A NEAREST NEIGHBOR ANALYSIS FOR US.

A. UH-HUH.

Q. IS THAT RIGHT?

A. THAT'S RIGHT.

Q. AND WAS HE GETTING THE PRODUCT THAT HE EXPECTED TO GET?

A. I THINK THE ANALYSIS WAS A T4 ENZYME WAS NOT AS GOOD AS HE EXPECTED.

Q. THE QUESTION, SIR, WAS: WHEN DR. KLEPPE DID THIS, DID HE GET THE PRODUCT HE EXPECTED TO GET?

A. AS I SAID --

MR. FIGG: YOUR HONOR, DR. VAN DE SANDE ANSWERED THE QUESTION. I THINK THERE'S BEEN A CONTINUING HARASSMENT OF THE
WITNESS. HE ANSWERS THE QUESTION AND MR. PASAHOW REASKS THE
QUESTION OVER AND OVER AGAIN.

THE COURT: IT'S ESSENTIALLY THE SAME QUESTION AND THE
SAME ANSWER.

YOU'RE NOT GETTING AN ANSWER? IS THAT YOUR VIEW?

MR. PASAHOW: I'M NOT SURE THAT THE LAST ANSWER
INDICATED AN AFFIRMATIVE OR NEGATIVE RESPONSE, YOUR HONOR.

THE COURT: I THINK HE GAVE YOU AN ANSWER, THOUGH.

THE OBJECTION, THEN, IS SUSTAINED, SO LET'S MOVE ON.

Q. (BY MR. PASAHOW) WELL, THE QUESTION, SIR, IS: IS THIS
NEAREST NEIGHBOR ANALYSIS HERE THE NEAREST NEIGHBOR ANALYSIS
THAT YOU'D EXPECT IF WHAT YOU DID WAS USED THE DNA-II AND THE
NINE-BASE PRIMER AND THE 10-BASE PRIMER AND YOU GOT PRODUCT BY
HAVING THEM EXTEND?

A. IF YOU WOULD HAVE HAD ONLY PRIMER EXTENSION, I WOULD HAVE
EXPECTED TO SEE A DIFFERENT NEAREST NEIGHBOR.

(PAUSE IN PROCEEDINGS)

THE COURT: COUNSEL, PERHAPS WHILE YOU'RE DOING THAT,
THIS IS A GOOD TIME TO BREAK. IT'S ALREADY 12:00. SO WE'LL
TAKE ABOUT 10 MINUTES.

PLEASE FOLLOW THE INSTRUCTIONS I'VE GIVEN YOU, AND
WE'LL SEE YOU AT THE CLOSE OF THE RECESS.

YOU MAY STEP DOWN.

(JURY_excused)

(RECESS TAKEN AT 12:01 P.M.)
MR. PASAHOW: THANK YOU, YOUR HONOR.

Q. DR. VAN DE SANDE, ONE POINT WHICH APPARENTLY ISN’T CLEAR
ABOUT EXHIBIT 68 WE HAVE OVER ON THE SCREEN HERE, WE WERE
TALKING ABOUT THIS CHART. THAT’S A CHART OF EXPERIMENTS WHERE
DR. KLEPPE WAS TRYING TO MEASURE THE EFFECT OF PH AND THE EFFECT
OF TEMPERATURE OF THE DE NOVO SYNTHESIS REACTION?
A. NO, THAT’S NOT COMpletely CORRECT. HE WAS TRYING TO MEASURE
THE EFFECT OF PH AND TEMPERATURE ON SYNTHESIS OF ALTERNATING AT
AND THE PRESENCE OF INPUT ALTERNATING AT, THAT’S NOT THE DE NOVO
SYNTHESIS.

Q. THE POINT OF THE EXPERIMENT WAS TO TRY TO INVESTIGATE THE
CONDITION THAT WOULD AFFECT THE DE NOVO SYNTHESIS REACTION?
A. I THINK WHAT HE WAS TRYING TO DO IS INVESTIGATE THE
CONDITION WHERE, NUMBER ONE, THE EFFECT OF PH ON THE DNA
SYNTHESIS IN GENERAL AND THE EFFECT OF TEMPERATURE ON DNA IN
GENERAL. THERE’S NO INDICATION OF DE NOVA SYNTHESIS.

Q. DO YOU RECALL WE DISCUSSED THIS IN YOUR DEPOSITION?
A. YES, THAT WAS BEFORE I’D SEEN THE EXPERIMENTS.

Q. AT THAT POINT I ASKED THE QUESTION, BEGINNING LINE 12, PAGE
35, REFERRING TO THIS:

DO YOU UNDERSTAND THAT -- YOU SAID I WOULD UNDERSTAND
THIS TO MEAN THAT IN THE WORK USING THE E. COLI, DNA POLYMERASE,
THAT INITIATION IN THIS REFERS TO THE GRAPH ON THE RIGHT-HAND
SIDE OF THE DE NOVO SYNTHESIS OF ALTERNATING AT, E. COLI
POLYMERASE HAS THE ABILITY TO DE NOVO SYNTHESIS THE POLYMER
ALTERNATING AT IN THE ABSENCE OF ANY TEMPLATE OR PRIMER.

WHAT WAS DONE HERE IN THIS EXPERIMENT?

THE WAY UNDERSTAND IT FROM THE NOTES HERE IS THAT THE

EFFECT OF PH AND THE EFFECT OF TEMPERATURE WAS INVESTIGATED ON

THE DE NOVO SYNTHESIS OF ALTERNATING AT.

THEN I ASKED, SO THE GRAPH TO THE RIGHT OF THAT NOTE

REFERS TO EXPERIMENTS ON DE NOVO SYNTHESIS?

YOU SAID THAT’S THE WAY I INTERPRET IT.

A. THAT’S EXACTLY THE WAY I INTERPRETED FROM HIS GRAPH. I HAVE

BEEN ABLE TO SEE THE EXPERIMENTS THAT RELATE TO THAT, THE

EXPERIMENTS CLEARLY INDICATE THE THERE WAS INPUT.

Q. SO SOMETIMES THE EFFORTS TO INTERPRET THIS HISTORICAL DATA

ISN’T ENTIRELY ACCURATE THE FIRST TIME AROUND?

A. NOT IF YOU DON’T HAVE ALL THE FIGURES IN FRONT OF YOU, NO.

Q. JUST BEFORE THE BREAK WE WERE TALKING ABOUT EXPERIMENTS 40

AND THE NEAREST NEIGHBOR ANALYSIS AND AGAIN HE WE TRIED TO CHART

IT OUT IN HOPES OF MAKING IT A BITS CLEARER.

AS I UNDERSTAND IT WHAT HAPPENS IN 48 IS AGAIN WE START

OUT WITH DNA-II AND THE TWO NC’S GET FILLED IN AND THEN WE HAVE

PRIMERS AND THE PRIMERS EXTEND ADDING RADIOACTIVE C’S, GOT IT

RIGHT SO FAR?

A. CORRECT.

Q. THEN, AS I UNDERSTAND THE NEAREST NEIGHBOR ANALYSIS, WHAT WE

LOOK TO IS THE LETTER JUST BEFORE THE RADIOACTIVE C?

A. YES. THAT’S WHAT TECHNIQUE INDICATES, RIGHT.
Q. SO THE NEAREST NEIGHBOR ANALYSIS COUNTS THE NUMBER OF TYPES
OF EACH LETTER ADDED JUST BEFORE A C?
A. THAT'S RIGHT.
Q. AND HERE WHAT WE'VE DONE IS TO COLOR ALL THOSE IN RED AND,
OF COURSE, IT ONLY AFFECTS THE LETTERS ON THE DNA THAT GETS
MADE --
A. ONLY AFFECTS THE LETTERS WHICH ARE ADJACENT TO THE C'S AS
INDICATE ON THE DNA WHICH IS MADE, CORRECT.
Q. IT'S A IT'S ADJACENT, ADDED JUST BEFORE THE C?
A. CORRECT.
Q. THEN WE COUNTED UP ALL THE RED LETTERS AND THAT WOULD HAVE
GOTTEN IN THIS EXPERIMENT 40 A AND, AS I UNDERSTAND WHAT YOU DO,
YOU CALCULATE THE RATIO OF THOSE?
A. YES.
Q. THEN YOU CALCULATE THE OBSERVER RATIO?
A. YES.
Q. AND YOU HOPE THEY'RE ESSENTIALLY IF SAME?
A. THAT'S WHAT YOU HOPE FOR, RIGHT.
Q. HERE INSTEAD OF GETTING RATIOS THAT WERE ESSENTIALLY THE
SAME YOU GOT SOME WIDE DIVERGENCE?
A. RIGHT.
Q. SO AT LEAST IN EXPERIMENT 48 WHEN HE USED DNA-II AND THE
NINE BASE PRIMER AND THE TEN BASE PRIMER DID YOU NOT GET THE
PRODUCT HE INTENDED?
A. IN THIS PARTICULAR EXPERIMENT I THINK DR. KLEPPPE NICELY
SHOWED WHY WE DON'T USE THE 48 POLYMERASE TODAY. IT'S NOT BEING
USED AT ALL. I THINK THIS VERY CLEARLY IDENTIFIES WHY NOT.
Q. DR. KLEPPPE THEN WENT ON IN HIS NEXT EXPERIMENT DID A CONTROL
TO FIND OUT IF THE T4 POLYMERASE WOULD GENERATE THE RIGHT
RESULTS IN A REACTION WHERE HE COULD CONTROL WHAT HAPPENED; IS
THAT RIGHT?
A. YES.
Q. AND THAT'S EXPERIMENT 49?
A. 49.
Q. IN 49 HE JUST PUT IN DNA-II?
A. YES.
Q. AND HE JUST ADDED THE TWO C'S?
A. YES.
Q. AND HE LOOKED TO SEE IF MOST OF HIS RADIOACTIVITY WAS IN
THAT G AND THAT T?
A. YES.
Q. SO WHAT ONE HAVE EXPECTED FROM THAT EXPERIMENT WAS MOST OF
THE RADIOACTIVITY FROM THE NEAREST NEIGHBOR ANALYSIS IN THE G'S
AND IN THE T'S?
A. HE WOULD EXPECT ONE TO ONE RATIO.
Q. GET THE RIGHT PART OF THIS UNDER HERE, THAT'S ESSENTIALLY
WHAT HE GOT, RIGHT?
A. RIGHT. HE GOT SOME BACKGROUND IN C AND SOME BACKGROUND IN
A.
Q. HE GOT 614 COUNTS IN A, 715 COUNTS IN G, 7,769 COUNTS IN T,
Q. AND THAT WOULD BE A NEAREST NEIGHBOR ANALYSIS THAT UNDER THE EXPERIMENTAL ERROR OF THE TIME WOULD CONSIDER TO BE A CORRECT RESULT?

A. IT WOULD BE WITH QUITE A GOOD RESULT, RIGHT.

Q. SO AT LEAST WHEN HE USED HIS T4 POLYMERASE ON A SYSTEM WHERE HE KNEW HOW IT WOULD COME OUT, IT CAME OUT, RIGHT?

A. RIGHT.

Q. CHANGE THE SUBJECT HERE NOW.

YOU TALKED ABOUT CLAIM 17 DURING YOUR DIRECT EXAM. LET ME SHOW YOU CLAIM 17 OF THE '202 PATENT.

A. YES.

Q. AND IT REFERS TO THE PROCESS OF CLAIM 1 WHERE IN AT LEAST ONE PRIMER CONTAINS AT LEAST ONE NUCLEOTIDE WHICH IS NOT COMPLIMENTARY TO THE SPECIFIC SEQUENCE TO BE AMPLIFIED?

A. RIGHT.

Q. DO YOU BELIEVE THAT THAT CLAIM WAS SOMETHING THAT DESCRIBES A PROCESS THAT WAS DONE IN THESE EXPERIMENTS WE'RE TALKING ABOUT?

A. IN THIS PARTICULAR EXPERIMENT IT WAS DUPLEX II, ONE OF THE BASIS, IS NOT BASE PAIRS.

Q. AND BY THAT WHAT YOU MEAN IS, FOR EXAMPLE, WHEN YOU PUT ON THIS PRIMER HERE THIS G IS GOING TO STICK OUT AT THE END?

A. NO. USUALLY SHOWN ON THE TOP STRANDS. THAT OBVIOUSLY IF
YOU PUT ON THE PRIMER WHICH IS CORRESPONDING TO THE NONA DCCTCCA
WHICH YOU HAVE BELOW IN GREEN THAT YOU’RE MISSING THE ONE BASE
IN THE TOP STRAND.

Q. THAT’S THIS C?
A. THE C AND THE SAME ON THE OTHER SIDE, YES.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. PASAHOW) SO YOU TAKE THIS LANGUAGE NOT
COMPLIMENTARY TO THE SPECIFIC SEQUENCE TO BE AMPLIFIED TO
INCLUDE THE CASE WHERE ONE OF THE BASIS IS MISSING?
A. THIS IS ONE POSSIBLE INTERPRETATION.

Q. AND THE OTHER POSSIBLE INTERPRETATION IS IT REQUIRES A
MISMATCH?
A. COULD BE A MISMATCH, YES.

Q. NOW, WE’VE GONE THROUGH EXPERIMENT 49 AND FOUND DR. KLEPPE’S
STILL DOING SOME CONTROLS ON THESE DNA-II TEN BASE PAIR, NINE
BASE PAIR EXPERIMENTS. AND YOU TOLD US THAT IN THE FALL DR.
KHORANA HAD THIS GROUP OF FOUR OF YOU START WORKING MORE THAN
FULL TIME --
A. YES.

Q. -- ON TRYING TO ASSEMBLE THE GENE?
A. VERY MUCH SO.

Q. YOU TOLD US THAT, OF COURSE, STOPPED DR. KLEPPE FROM DOING
REPAIR REPLICATION REACTIONS?
A. WELL, IT STOPPED HIM. I THINK YOU HAD THE OCCASION TO USE
SOME OF THE DUPLEXES WHICH HE ALSO PREPARED, TO DO SOME SITE
REACTIONS AS I DISCUSSED BEFORE TO LOOK AT THE THE INCORPORATION, BUT I WOULD SAY 90 PERCENT OF HIS EFFORT WAS LOOKING AT GENE SYNTHESIS.

Q. WHEN DID THAT GENE SYNTHESIS EFFORT GET DONE?
A. I THINK IT WAS AROUND APRIL, MAY, I THINK, 1970.

Q. SO HE WENT FROM FALL OF 1969 TO APRIL, MAY, '70 ON THE GENE SYNTHESIS?
A. YES.

Q. AFTER THAT DID DR. KLEPPE GET BACK TO HIS REPAIR REPLICATION WORK?
A. HE DID A FEW MORE REPAIR REACTIONS, YES.

Q. DID HE DO ANYMORE CONTROLS RELATING TO THE USE OF DNA-II, TRYING TO FIGURE OUT WHAT HAPPENED?
A. I CAN'T RECALL. I WOULD HAVE TO LOOK AT HIS NOTES.

Q. WELL, IN PREPARING FOR YOUR TESTIMONY DID YOU TRY AND PULL OUT THE SIGNIFICANT CONTROL EXPERIMENTS?
A. NO, I PULLED OUT EXPERIMENTS WHICH I DESCRIBED, WHICH IS NUMBER 329 AND EXPERIMENT 28.

Q. WHAT WOULD YOU NEED TO LOOK AT TO DETERMINE WHETHER THERE WERE ANY OTHER CONTROLS?
A. TO LOOK AT THE NOTEBOOKS.

Q. WE'RE TALKING ABOUT THE PERIOD AFTER APRIL, MAY 1970?
A. CORRECT.

Q. DO YOU RECALL ANY EXPERIMENTS THAT HE DID AFTER HE RETURNED TO HIS REPAIR REPLICATION WORK?
A. THAT WAS JUST A TIME THAT I THINK HE WAS TRYING TO
MANUSCRIPT ALL READY. THE MANUSCRIPT WAS '71 KLEPPE, ET AL.
PAPER AND I'M SURE THERE WAS OUTSTANDING THINGS HE WAS TRYING TO
FINISH AT THAT PARTICULAR TIME BEFORE HE WENT BACK TO NORWAY.

Q. WHEN DID HE RETURN TO NORWAY?
A. I THINK HE LEFT . . . I WOULD SAY, AROUND . . . I THINK HE
LEFT AROUND JULY 1970.

Q. NOW, ONE WAY TO FIND OUT WHETHER YOU'RE USING THE PRODUCT OF
ONE REACTION AS TEMPLATE AND ANOTHER REACTION WOULD BE TO TAKE
IT STEP BY STEP. LET ME EXPLAIN WHAT I MEAN.

YOU COULD START WITH, SAY, THE BOTTOM HALF OF DNA-II
ALONE AND PUT ON THE PRIMER, OBVIOUSLY USING A A LOT OF
MOLECULES AND THEN EXTEND IT AND THEN SEE IF YOU COULD USE THE
PRIMER FOR THIS STRAND IN A SEPARATE CYCLE AND COME BACK THE
OTHER WAY?

A. YES.

Q. DID YOU EVER SEE ANY EXPERIMENTS USING THAT SORT OF CONTROL?
A. I DON'T THINK SO.

Q. DO YOU KNOW WHY THAT KIND OF EXPERIMENT WASN'T DONE?
A. I THINK DR. KLEPPE RAN OUT OF TIME, I THINK.

Q. SO YOU THINK THERE MIGHT HAVE BEEN SOME CONTROLS DR. KLEPPE
HAD IN MIND HE DIDN'T HAVE TIME TO DO?
A. DEFINITELY SOME EXPERIMENTS IF HE WOULD HAVE TIME TO PURSUE
THE CYCLED REACTIONS WOULD HAVE DONE, YES.

Q. THEN PERHAPS WOULD HAVE GOTTEN THOSE TO THE POINT WHERE HE
AND DR. KHORANA WOULD BE PREPARED TO PUBLISH THEM?
A. IF HE WOULD HAVE HAD THE TIME FOR THAT, YES.

MR. PASAHOW: NOTHING FURTHER, YOUR HONOR.

THE COURT: THANK YOU.

(PAUSE IN THE PROCEEDINGS)

MR. FIGG: EXCUSE ME, JUST ONE SECOND.

(PAUSE IN THE PROCEEDINGS)

REDIRECT EXAMINATION

BY MR. FIGG:

Q. DR. VAN DE SANDE, DO YOU REMEMBER MR. PASAHOW ASKING YOU
ABOUT DR. RUTH KLEPPE'S SEMINAR NOTES IN WHICH SHE INDICATED THE
AMOUNTS OF PRIMERS THAT WERE AVAILABLE IN THE LABORATORY?
A. YES. THE NOTES FROM THE SEMINAR DR. KHORANA GAVE, I THINK,
ON DECEMBER 7TH 1969.

Q. WHAT HAPPENED WITH THAT INVENTORY OF PRIMERS BETWEEN 1969
AND 1972?
A. AS I MENTIONED ON THE LAST QUESTIONS MR. PASAHOW ASKED ME,
THE GENE SYNTHESIS WAS FINISHED BY ABOUT APRIL, MAY, SO MAJOR
AMOUNT OF THE OLIGONUCLEOTIDES WERE, OF COURSE, UTILIZED IN THE
GENE SYNTHESIS AND ALL THE EXPERIMENTS LEADING UP TO THE SECOND
SUCCESSFUL COMPLETION OF THE PROGRAM.

Q. SO THEY WERE -- THEY WERE -- THE ONES LISTED IN THAT
INVENTORY, THERE'S NO REASON TO ASSUME THEY WERE STILL AROUND IN
1972 WHEN MR. MOLINEUX WAS DOING HIS WORK?
A. NOT IN THOSE QUANTITIES, DEFINITELY NOT.
Q. DOCTOR, MR. PASAHOW ASKED YOU A GREAT NUMBER OF QUESTIONS ABOUT HAIRPINS?
A. YES.
Q. BEGINNING TO SOUND LIKE WE WERE IN A BEAUTY PARLOR RATHER THAN A COURTROOM.
AND I BELIEVE, IF I RECALL CORRECTLY, HE ASKED YOU IF IT WAS POSSIBLE SOME OF THE DUPLEX WOULD BE IN HAIRPIN FORM IN THE EXPERIMENTS THAT YOU DESCRIBED FROM DR. KLEPPE'S NOTEBOOKS, DO YOU RECALL THAT?
A. YES, I DO.
Q. IF SOME OF THE DUPLEX WAS IN THE HAIRPIN FORM, IS IT . . . WHAT HAPPENS WITH THE REST OF THE DUPLEX THAT'S NOT IN THE HAIRPIN FORM?
A. THE REST OF THE DUPLEX WOULD BEGRING PRIMER, THERE WOULD BEEN TEMPLATE PRIMER ORIENTATION.
Q. AND WHAT WOULD BE THE EFFECT OF THAT ON THE COURSE OF THE REACTION?
A. WELL, THE YIELD WOULD BE LESS, THE EFFICIENCY WOULD BE LESS. THAT WOULD BE ONE OF THE MAJOR THINGS AND ALWAYS THE HAIRPIN WOULD FILL OUT TO FORM NOW A COMPLETE HAIRPIN INSERT INSTEAD OF A PARTIAL HAIRPIN WHICH IS A STABLE STRUCTURE AND PROBABLY NOT COMPLETE IN THE REACTION, NORMALLY REFER TO AS SNAP-BACK DNA IT WOULD STAY LIKE THAT AFTER A HEAT CYCLE.
Q. AND DO YOU BELIEVE THAT DR. KLEPPE'S EXPERIMENTS THAT YOU HAVE DESCRIBED WERE OPERATING AT A HUNDRED PERCENT EFFICIENCY?
A. NO, NOT AT ALL.  

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) DR. VAN DE SANDE, DO YOU STILL HAVE THE '202 PATENT THERE?

A. I DON'T THINK I EVER HAD IT HERE.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) LET ME REMEDY THAT AND GIVE YOU A COPY OF WHAT WE'VE MARKED AS EXHIBIT A-1, THE '202 PATENT.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) DR. VAN DE SANDE, DO YOU SEE ANYTHING IN THE '202 PATENT THAT REQUIRES THAT THE CYCLED REACTION WE'VE BEEN TALKING ABOUT GOES TO A HUNDRED PERCENT COMPLETION ON EACH CYCLE?

A. NOT AT ALL. THERE'S NO DISCUSSION OF YIELD IN THIS PARTICULAR CLAIM OR ANY OTHER CLAIMS.

Q. DOES THE PATENT SAY ANYTHING ABOUT THE EFFICIENCY THAT'S REQUIRED FOR THE REACTION TO BE ENCOMPASSED WITHIN THE PROCESS DESCRIBED IN THE PATENT?

A. IT DOES NOT.

Q. ARE THERE ANY EXAMPLES IN THE PATENT THAT INDICATE WHAT THE EFFICIENCY IS IN THE REACTION?

A. I THINK THERE WAS ONE EXAMPLE, PAGE 23 LINE 27 WHERE THE YIELD PER CYCLE WAS GIVEN AS 61.9 PERCENT, JUST OVER 60 PERCENT.

Q. AND MAY HAVE ANTICIPATED MY QUESTION, BUT WHAT EFFICIENCY OF REACTION DO YOU FEEL IS DEFINED BY THIS CLAIM?
A. THERE'S NO EFFICIENCY DEFINED AT ALL.

Q. SO COULD IT BE 10 PERCENT, 20 PERCENT?

A. COULD HAVE BEEN 10 PERCENT, YES. COULD BE FIVE PERCENT, COULD BE ANY PERCENTAGE, COMPLETELY OPEN.

Q. NOW, I FELT THERE WAS SOME CONFUSION ABOUT WHAT DR. MULINEUX' EXPERIMENTS WERE SHOWING IN CONNECTION WITH THE TEMPLATE OR -- EXCUSE ME, THE HAIRPIN FORMATION. AM I CORRECT, DOCTOR MULINEUX WAS DOING EXPERIMENTS WITH A TEN FOLD EXCESSIVE PRIMER AND DETERMINING WHAT IMPACT THAT HAD ON THE TENDENCY OF DNA-II TO FORM A HAIRPIN?

A. THAT'S RIGHT.

Q. AND AGAIN CAN YOU SUMMARIZE WHAT DR. MULINEUX' FINDING WERE IN THAT REGARD?

A. I THINK HIS FINDINGS WERE THAT IN THE ABSENCE OF PRIMER HE WOULD SEE ABOUT 40 PERCENT HAIRPIN FORMATION AND HE WAS CITING EXCESS OF PRIMERS SUCH AS TEN FOLD HE EXCESS. THAT THE DEGREE OF HAIRPIN FORMATION WAS DECREASED BY 27 PERCENT, THIS IS 27 PERCENT OF THE 40 PERCENT.

Q. SO WHEN HE JUST HAD THE DUPLEXES IN THERE AND NOT -- NO PRIMER OR ANYTHING, HOW MUCH OF THE TEMPLATE WAS IN HAIRPIN FORM?

A. HE STATED AROUND 40 PERCENT.

Q. AND THE THE REST OF IT WAS IN WHAT FORM?

A. WOULD HAVE BEEN IN A DUPLEX FORM.

Q. AND THEN WHEN HE ADDED A TEN FOLD EXCESS OF PRIMER THAT 40
PERCENT WENT TO THE OTHER NUMBER?
A. WENT DOWN TO, YOU KNOW, ABOUT 70 PERCENT OF 40, WHICH IS
ABOUT 28 PERCENT. WHICH WOULD MEAN THAT, IN ESSENCE, 72 PERCENT
IS IN ORIENTATION.
Q. AND IN THE GRAPHS THAT MR. PASAHOW SHOWED YOU IN THE KLEPPE
PAPER DID THEY USE THIS, DID THOSE GRAPHS DESCRIBE EXPERIMENTS
USING THE SAME TEN TO ONE EXCESSIVE PRIMERS THAT DOCTOR MOLINEUX
WAS EXPERIMENTING WOULD?
A. I THINK THERE ARE TWO DIFFERENCES IN THE EXPERIMENTS. FIRST
OF ALL, DR. KLEPPE USED THE SEPARATED STRANDS BY THEMSELVES AND
SECONDLY HE ONLY USED A TWO-FOLD EXCESS OF PRIMER.
Q. MR. PASAHOW ASKED YOU A NUMBER OF QUESTIONS ABOUT NEAREST
NEIGHBOR ANALYSIS, DO YOU RECALL DR. MOLINEUX' SUMMARY THAT HE
GAVE TO DR. KHORANA?
A. RIGHT.
Q. THAT WAS EXHIBIT A-174.
A. YES.
Q. AND DID DR. MOLINEUX REPORT NEAREST NEIGHBOR ANALYSIS IN
THAT EXHIBIT?
A. YES, HE DOES.
Q. DO YOU STILL HAVE THAT EXHIBIT?
A. WHEN HE WAS TALKING ABOUT IT. I DON'T THINK I HAVE IT HERE.
Q. LET ME SHOW YOU MY COPY OF THAT EXHIBIT.
YOU CONFIRM DR. MOLINEUX DID INDEED DO NEAREST NEIGHBOR
ANALYSIS ON THIS PRODUCT?
A. YES, HE DID THE NEAREST NEIGHBOR AFTER THE FIRST CYCLE, 
AFTER THE FINAL POINT OF THE REACTION THERE ARE SEVERAL NEAREST 
NEIGHBOR ANALYSIS INDICATED.

Q. WHAT DO THOSE NEAREST NEIGHBOR ANALYSIS INDICATE TO YOU?
A. NEAREST NEIGHBOR ANALYSIS IN THIS EXPERIMENT ARE IN THE 
AGREEMENT WITH THE EXPECTATION TWO TO ONE RATIO IN THIS CASE CP 
TO CG IN THE ONE EXPERIMENT.

THE SAME IN THE OTHER ONES THE RATIO THAT HE EXPECTED WAS VERY CLOSE TO TWO TO ONE RATIO, AT LEAST FOUR NEAREST 
NEIGHBOR ANALYSIS SHOWN HERE.

Q. DO THOSE DATA REPORTED IN THERE GIVE YOU ANY INDICATION OF 
WHETHER REPLICATION WAS OCCURRING BY PRIMER ELONGATION OR BY 
SOME OTHER STRUCTURE?
A. IT WOULD HAVE TO BE PRIMER ALONGATION IN THIS PARTICULAR 
CASE BECAUSE THOSE STRUCTURES REALLY COULD NOT FORM ANY HAIRPINS 
AS WE HAVE BEEN TALKING ABOUT WITH DUPLEX II.

Q. DOCTOR, I'VE PLACED ON THE EASEL A COPY OF PAGE 5220 FROM 
THE PANET PAPER, THAT'S BEEN MARKED AS EXHIBIT A-19. DO YOU 
FIND ANYTHING IN THAT EXCERPT ON PAGE 5220 THAT INDICATES 
WHETHER THE KHORANA LABORATORY CONCLUDED FROM THEIR EXPERIMENTS 
WHETHER REPLICATION WAS OCCURRING BY PRIMER ELONGATION OR BY 
HAIRPIN OR BY ONE OF THESE OTHER STRUCTURES THAT MR. PASAHOW WAS 
ASKING YOU ABOUT?
A. NO, I THINK IN THE PART OF THE DESCRIPTION PAPER BY PANET 
CLEARLY INDICATES THAT THE REPLICATION WAS SUCCESSFUL, THAT
DEPENDANT VERY MUCH ON THE PRIMERS TO THE TEMPLATE RATIO AND ONE COULD CARRY OUT MULTIPLE CYCLES OF REPAIR.

ALSO INDICATED, IN ESSENCE, HE WANTED TO MAINTAIN APPROPRIATE PRIMER TEMPLATE RATIOS AND ALL THIS IS IN SUPPORT OF THE EXPERIMENTS WHICH DR. MOLINEUX DESCRIBED.

WE ALSO WENT THROUGH TODAY, IN ESSENCE, MY UNDERSTANDING THIS PARTICULAR STATEMENT IS COMING FROM THE EXPERIMENTS WHICH WERE CARRIED OUT BY DR. MOLINEUX WHICH HE DESCRIBED HERE WHICH WE ALSO SPEND TIME TALKING ABOUT TODAY.

Q. MR. PASAHO also asked you about your analysis of Dr. Kleppe’s data and he asked you whether you had factored in the amount of liquid that would have been added to the reaction had you assumed the addition of DNA polymerase, do you recall that?

A. YES, I DO.

Q. IF YOU ADD THAT AMOUNT OF LIQUID INTO YOUR CALCULATIONS WHAT WOULD HAVE BEEN THE IMPACT ON THE RESULTS?

A. THE IMPACT WOULD HAVE BEEN THE COUNTS WOULD HAVE INCREASED AND SEE MORE INCORPORATION OF DNA IF I WOULD HAVE COUNTED.

Q. SO, IN EFFECT, YOU UNDERESTIMATED THE AMOUNT OF INCORPORATION?

A. AS I SAID, I WANTED TO BE CONSERVATIVE IN MY CALCULATIONS.

Q. ACTUALLY WOULD HAVE BEEN A VERY TINY AMOUNT, HOW MUCH ENZYME WAS DR. KLEPPE ADDING TO HIS REACTION?

A. ONE MICROLITER. VERY SMALL AMOUNT.

Q. HOW MUCH WAS THE TOTAL VOLUME?
A. ANYWHERE FROM 50 TO 90 MICROLITERS.
Q. COULD EFFECT ON THE DILUTION?
A. TWO PERCENT DOWN.
Q. MR. PASAHOW ALSO ASKED YOU ABOUT THE ADDITION OF LIQUID IN EXPERIMENT 28, DO YOU RECALL THAT?
A. YES, I DO.
Q. DO YOU STILL HAVE THAT THE EXHIBIT NUMBER A . . . 70 UP THERE, DR. KLEPPE'S NOTEBOOK TWO AND THREE.
A. I HAVE TWO AND THREE ONES HERE.
Q. I'M SORRY, THAT WAS EXHIBIT A-71.
A. YES, THIS IS PAGE 47 OF THE NOTEBOOK.
Q. THAT'S RIGHT. WOULD YOU TURN TO PAGE 48 OF THE NOTEBOOK.
NOW, I THINK YOU REFERRED TO IT AS A COCKTAIL DESCRIBED ON THE TOP OF THE PAGE THERE?
A. YES.
Q. DID HE USE ALL OF THAT COCKTAIL SOLUTION THAT HE MADE UP IN THE ENSUING EXPERIMENT?
A. HE DID NOT USE IT ALL IN THE FIRST CYCLE. HE USED PART OF IT.
Q. SO IF THERE HAD BEEN ADDITIONAL LIQUID ADDED IN THAT COCKTAIL WOULD IT HAVE MADE ANY DIFFERENCE AT ALL IN CONNECTION WITH THE DILUTION FACTORS YOU USED IN YOUR CALCULATIONS?
A. AGAIN, IT WOULD HAVE SLIGHTLY DILUTED MY FACTOR A LITTLE BIT. AGAIN BY A COUPLE OF PERCENT, NOT VERY MUCH, VERY SMALL PERCENTAGE.
Q. AGAIN, IT WOULD HAVE HAD THE IMPACT OF UNDERESTIMATING?
A. THAT'S CORRECT.

Q. NOW, IN EXPERIMENTS THREE THROUGH NINE MR. PASAHOW, I BELIEVE, ASKED YOU ABOUT THE FACT THERE WERE CONTROLS DONE THERE IN BETWEEN EXPERIMENTS THREE AND NINE.
A. YES.

Q. WERE THOSE SERIAL REACTIONS?
IN OTHER WORDS, DID THOSE CONTROLS RESULT FROM THE TAKING OF THE SOLUTION FROM THE PREVIOUS REACTION AND THEN DOING SOMETHING ELSE WITH IT?
A. NO, EXPERIMENTS FOUR, FIVE, SIX, SEVEN AND EIGHT WERE ALL SEPARATE REACTIONS.

Q. HE MADE THOSE ALL UP FRESH?
A. ALL SET UP SEPARATELY, YES.

Q. NOW, EXPERIMENT 28 ONE THROUGH SIX, DID HE MAKE UP TOTALLY NEW REACTIONS ON EACH OF THOSE OR WERE THOSE SERIAL REACTIONS?
A. THAT WAS A SERIAL REACTION WHICH WENT THROUGH, IN ESSENCE, SIX STEPS.

Q. DOES THAT FACT HAVE ANY IMPACT ON YOUR CONCLUSION THAT THESE FEW OMISSIONS THAT APPARENTLY DR. KLEPPE MADE IN HIS NOTEBOOK WERE IN FACT JUST TYPOS OR ACCIDENTS RATHER THAN THE ACTUAL EXPERIMENTAL DESIGN?
A. YES, THE EXPERIMENTAL DESIGN WAS TO CARRY OUT CYCLED REACTIONS. AND LOOKING AT THE RESULTS DR. KLEPPE WAS SUCCESSFUL IN THOSE.
Q. DR. VAN DE SANDE, I'VE PLACED THE POSTER WHICH CONTAINS YOUR CALCULATIONS OF DR. KLEPPE'S RESULTS IN EXPERIMENT 28 ON THE EASEL. DO YOU BELIEVE THIS IS A FAIR REPRESENTATION OF THE DATA THAT'S PRESENTED IN DR. KLEPPE'S NOTEBOOK?
A. I THINK SO.

Q. NOW, ON THIS MATTER OF THE SPECIFIC ACTIVITY IN EXPERIMENT FOUR ON PAGE 48 OF DR. KLEPPE'S NOTEBOOK, I THINK YOU INDICATED THAT THE IMPACT OF THAT WOULD HAVE BEEN AT ONE POINT IN THIS SERIES OF EXPERIMENTS?
A. YES.

Q. IF DR. KLEPPE INDEED DID CHANGE THE RULE MID-COURSE DURING HIS EXPERIMENT?
A. RIGHT.

Q. WOULD IT HAVE AFFECTED THE RELATIONSHIP BETWEEN REACTIONS ONE, TWO AND THREE?
A. THEY'RE REACTIONS ONE AND TWO WHICH WERE CARRIED OUT BEFORE THE ADDITION WOULD STILL INDICATE THERE'S AN INCREASE IN THE AMOUNT OF DNA SYNTHESIS. WHICH WOULD -- YOU KNOW, TO ME IMPLY AND MEAN THAT YOU WERE MAKING MORE TEMPLATE.

Q. WOULD IT AFFECT THE RELATIONSHIP BETWEEN THE REACTIONS THREE, FOUR AND FIVE?
A. WOULD APPLY TO THAT PART, YES.

Q. WHAT WAS THE IMPORTANCE OF THE SPECIFIC ACTIVITY OF THE THIS RADIOACTIVE BUILDING BLOCK DR. KLEPPE WAS USING TO HIS ABILITY TO INTERPRET HIS EXPERIMENTS?
A. YOU HAVE TO USE CONSTANT SPECIFIC ACTIVITY THROUGHOUT
ESPECIALLY. YOU KNOW, A SERIES OF REACTIONS, A SERIAL REACTION
WHICH HE CARRIED OUT IN EXPERIMENT 28, OTHERWISE HE WOULD NOT
HAVE BEEN ABLE TO INTERPRET THE DATA.

Q. YOU MAKE THE ASSUMPTION THAT DR. KLEPPE HAD A SLIP OF THE
PEN THERE JUST SO THE DATA FITS THIS CURVE YOU'VE DRAWN?

A. NO, I'M NOT MAKING THAT ASSUMPTION AT ALL.

Q. WHAT'S THE BASIS FOR YOUR ASSUMPTION?

A. BASICALLY KNOWING TYPE OF EXPERIMENTALIST DR. KLEPPE WAS,
HAVING LISTENED TO HIS PRESENTATIONS ON THIS WORK, KNOWING WHAT
HIS INTERPRETATION OF HIS RESULTS WERE.

MR. FIGG: EXCUSE ME ONE MOMENT, YOUR HONOR.

THE COURT: YES.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) DR. VAN DE SANDE, I'D LIKE TO SHOW YOU A
DOCUMENT THAT'S BEEN MARKED AS EXHIBIT B-202, WHICH IS THE COPY
OF DR. KLEPPE'S NOTEBOOK ONE IN ITS ENTIRETY, AND PARTICULARLY
FOCUS YOUR ATTENTION ON PAGE 72 OF THAT NOTEBOOK.

IS THIS THE EXPERIMENT THAT IS REFERRED TO IN DR. RUTH
KLEPPE'S SEMINAR NOTES MR. PASAHOW WAS ASKING YOU ABOUT, EXHIBIT
68?

A. YES, THIS IS WHERE DR. KLEPPE CHECKS OUT THE CONDITIONS FOR
DNA POLYMERASE REACTIONS AND COMPARES PH 7.4 AND PH 6.9. IN
THIS PARTICULAR EXPERIMENT HE USES THE ALTERNATING POLYMER ATAT
AS ITS SUBSTRATE.
Q. IF I COULD USE MR. PASAHOW'S FANCY MACHINE HERE. DOES THIS INDICATE TO YOU WHETHER OR NOT THE NOTES THAT DR. RUTH KLEPPE TOOK RELATE TO DE NOVO SYNTHESIS AS MR. PASAHOW CALLED IT OR TO SOMETHING ELSE?

A. I THINK LOOKING AT THE EXPERIMENTS IN DR. KLEPPE'S NOTEBOOK IS VERY CLEAR THAT HE ADDED THE ALTERNATING AT POLYMER TO DO EXPERIMENTS.

Q. HIS PURPOSE FOR DOING THAT WAS TO STUDY THE ENZYME?

A. EXACTLY. HE CLEARLY STATES AT THE TOP IN ORDER TO TRY OUT CONDITIONS FOR THE DNA POLYMERASE REACTIONS THE ACTIVITY WAS COMPARED TO THE PL 7.4 AND 6.9 AT 37 DEGREES.

Q. THIS THE PHENOMENA CALLED DE NOVO SYNTHESIS -- UNDER WHAT CONDITIONS DOES THAT OCCUR?

A. IT OCCURS IF ONE TAKES DNA POLYMERASE 1 HAS AT LEAST A TWO-2 DEPORTION ATP, DEOXY TTP AND INCUBATES THE PRESENCE OF THE KORNBERG ENZYME FOR A VERY EXTENDED PERIOD.

I WOULD SAY I THINK THE FIRST EIGHT OR SO HOURS ONE SEES VERY LITTLE, IF ANYTHING. THEN VERY SLOWLY THE REACTION STARTS, BUT YOU WOULD HAVE TO INCUBATE THE SAME BATCH OF ENZYME FOR THAT LENGTH OF PERIOD.

Q. IN THE 14 HOURS OR SO YOU AND MR. PASAHOW COUNTED UP, WHAT'S THE EXTENT OF TIME FOR EXPERIMENT 28, DID THAT SITUATION EVER OCCUR, DID THE SAME SOLUTION OF ENZYMES SIT FOR 14 HOURS?

A. NO, OF COURSE, NOT. BECAUSE AT THE END OF EACH CYCLE THE REACTION WAS HEATED TO A HUNDRED DEGREES WHICH WOULD DESTROY
ENZYME.

Q. AND --

A. THAT'S WHY DR. KLEPPE HAD TO ADD NEW ENZYME FOR THE NEXT CYCLE.

Q. DR. VAN DE SANDE, DO YOU HAVE AN OPINION AS TO WHETHER OR NOT WHAT DR. KLEPPE WAS SAYING HERE WAS THIS PHENOMENA CALLED DE NOVO SYNTHESIS?

A. NOT AT ALL, HE WASN'T SEEING ANY DE NOVO SYNTHESIS.

Q. DO YOU HAVE AN OPINION AS TO WHETHER DR. KLEPPE IN THESE EXPERIMENTS AND DOCTOR MOLINEUX IN HIS EXPERIMENTS WAS SEEING PRIMER DEPENDENT REPLICATION OF THE DNA?

A. VERY MUCH SO. I THINK THEY SHOWED IN THEIR SERIES OF REACTIONS THAT THIS DNA SYNTHESIS PRIMER EXTENSION DEPENDED ON THE PRESENCE OF TEMPLATE, PRIMER AND HEAT CYCLE.

MR. FIGG: THANK YOU, DR. VAN DE SANDE. WE HAVE NO FURTHER QUESTIONS.

THE COURT: THANK YOU.

MR. PASAHOW.

MR. PASAHOW: YES, YOUR HONOR, I HAVE A FEW MORE, PLEASE.

RE CROSS-EXAMINATION

BY MR. PASAHOW:

Q. DR. VAN DE SANDE, AS WE'VE ALL BEEN TALKING ABOUT WHAT DR. MOLINEUX TOLD US I THOUGHT IT WOULD BE USEFUL TO GO AHEAD AND FIND WHAT HE DID TELL US. LET ME SHARE THAT WITH YOU AND THEN
I'D LIKE TO FIND OUT IF THAT'S WHAT YOU THINK HE TOLD US.

I ASKED HIM, WHAT I AM SAYING IS THAT YOUR FINDING WAS

WHEN YOU ADD DNA-II WITH THIS NINE BASE PAIR PRIMER IN THE RATIO

OF TEN MOLECULES OF PRIMER TO ONE MOLECULE OF TEMPLATE AND ABOUT

73 PERCENT OF THE CASES THE TOP STRAND FORMED A HAIRPIN AND

EXTENDED ON ITSELF WITHOUT ANY PRIMER BEING INVOLVED.

ANSWER, YES, THAT IS TRUE. THEN A PAUSE IN THE

PROCEEDINGS.

THEN I ASKED, THAT'S WHAT YOU REPORTED TO DR. KHORANA?

ANSWER -- NOW IT'S ABOUT THE EXHIBIT, HE SAID THAT'S

WHAT -- THAT'S WHAT THAT SUMMARY THERE SAYS, YES, AND IF I USED

A 20 FOLD EXCESS ONLY 40 PERCENT OF THAT HAIRPIN COULD BE

COMPETED OUT.

NOW, IS THAT WHAT YOU UNDERSTOOD DR. MOLINEUX BEEN

TELLING US?

A. I UNDERSTOOD DR. MOLINEUX TO TELL US THIS WAS 73 PERCENT OF

WHATEVER HAIRPIN FORMED.

Q. NOW, DID I UNDERSTAND YOU TO EXPLAIN TO MR. FIGG THAT IF WE

ASSUMED THAT WATER WAS ADDED WITH THE POLYMERASE IT HAD SOME

EFFECT ON THE NUMBER OF COUNTS THAT YOU CALCULATED IN THIS

EXHIBIT, THE SUMMARY OF DATA EXHIBIT?

A. THAT'S NOT WHAT WE DISCUSSED AT ALL.

Q. WHAT AFFECT DOES ADDING WATER HAVE ON YOUR CALCULATIONS?

A. WATER IS JUST PART OF THE NORMAL COCKTAIL OF THE VOLUME OF

THE REACTION. I DID NOT SAY THAT WATER HAD ANY AFFECT ON THE
CALCULATIONS. ALL THAT I SAID WAS THAT IF DNA POLYMERASE THE VOLUME OF DNA POLYMERASE ADDITION WOULD BE BROUGHT INTO THIS CALCULATION, THIS WOULD MEAN THAT MY REACTION HAD DILUTED MORE AND I WOULD HAVE TO CORRECT FOR THAT LITTLE BIT MORE OF DILUTION WHICH WAS, AS I SAID, ANYWHERE FROM ONE TO TWO PERCENT IN THAT RANGE.

Q. SO IF YOU CALCULATED IN THE POLYMERASE WAS ADDED IT WOULD CHANGE THE NUMBERS THAT YOU GRAPHEd?
A. VERY SLIGHTLY. ACTUALLY INCREASE THEM.

Q. NOW, THE POLYMERASE, OF COURSE, DOESN'T HAVE ANY RADIOACTIVE C'S IN THERE?
A. I HOPE NOT.

Q. HOW DOES THE ASSUMED PRESENCE OR ABSENCE OF THE POLYMERASE EFFECT -- LET ME START WITH SOMETHING ELSE.

OBVIOUSLY, THE ADDITION OR NON-ADDITION OF THE POLYMERASE WOULDN'T EFFECT WHAT THE MACHINE SHOWED -- THAT TAPE YOU SAID IT PRINTED OUT?
A. THE TAPE IS THERE.

Q. IT WOULDN'T EFFECT WHAT NUMBERS DR. KLEPPE TOLD US HE GOT?
A. THAT'S CORRECT.

Q. NOW, HOW WOULD THE ADDITION OF THIS POLYMERASE OR THE NON-ADDITION OF THIS POLYMERASE EFFECT WHAT YOU CALCULATED FROM THIS INFORMATION THAT THE MACHINE PROVIDED TO DR. KLEPPE AND THAT DR. KLEPPE WROTE DOWN?
A. RIGHT. IF YOU WOULD LOOK AT THE TABLE, FOR EXAMPLE, IN
COLUMN NUMBER 2, WHERE I SAY ADDED VOLUME IS 13 . . . THE WHITE LINE ADDED VOLUME THE SECOND COLUMN?

Q. HERE (INDICATING)?

A. YES.

Q. THAT WOULD HAVE INCREASED BY ONE. WHICH MEANS IT WOULD MAKE MY VOLUME VERY SLIGHTLY LARGER. SO MY CONCENTRATION OF THE DNA WOULD DECREASE, I WOULD HAVE TO ADJUST FOR THAT DILUTION FACTOR.

Q. YOU MEAN ADJUST IT BY CHANGING WHAT YOU MEAN BY NORMALIZE COUNTS HERE?

A. THAT'S CORRECT.

Q. WHAT ARE THEY NORMAL TO?

A. THEY'RE NORMALIZED, NORMALIZED TO THE STARTING VOLUME OF THE REACTION.

Q. NOW, AT THE END OF -- FIRST OF ALL, THIS GOES ONE TO SIX AND THIS GOES ZERO TO FIVE?

A. YES. BECAUSE ONE DID NOT INCLUDE THE HEAT STEPS, SO I ONLY INCLUDE THE HEAT STEPS BECAUSE THE FIRST ONE IS NOT AMPLIFICATION.

Q. SO ONE IS ZERO AND TWO IS ONE AND THREE --

A. RIGHT.

Q. NOW, UNDER YOUR NORMALIZES THE COUNTS THE END OF CYCLE ONE YOU'VE GOT 900 AND THE BEGINNING OF CYCLE TWO THE COUNTS ARE 803?

A. YES.

Q. WHAT HAPPENED TO THE COUNTS BETWEEN THE END OF CYCLE ONE AND
THE BEGINNING OF CYCLE TWO?
A. BECAUSE DR. KLEPPE TOOK A SAMPLE AT THE START OF REACTION TWO SINCE THE REACTION HAD DILUTED HE WOULD SEE LESS COUNTS.
Q. THERE SHOULD BE A KIND OF MATHEMATICAL CORRELATION BETWEEN THIS NUMBER (INDICATING) AND THIS NUMBER (INDICATING)?
A. THAT'S CORRECT.
Q. BASED UPON THE DILUTION?
A. THAT'S CORRECT.
Q. NOW, WE'VE TALKED ABOUT THE END OF FIVE AND THE BEGINNING OF SIX DR. KLEPPE SAYS HE USES SIX?
A. YES.
Q. SO WE DON'T KNOW IF HE USED 5A, OR 5B OR 5A AND 5B?
A. YES.
Q. AT THE END OF FIVE WE'VE GOT TWO DIFFERENT COUNTS HERE DEPENDING WHETHER YOU'RE TALKING ABOUT 5A OR 5B?
A. YES.
Q. SO IT'S LIKE YOU SAID YOU USED 5A?
A. 5A IS THE ONE SHOWN WITHOUT THE BRACKETS. 5B IS THE ONE SHOWN WITH THE BRACKETS.
Q. THE ONE YOU GRAPH DOWN HERE IS 5A?
A. THAT'S CORRECT.
Q. AT THE END OF CYCLE 5 OR 5A YOU GOT 11,000 COUNTS?
A. YES.
Q. AND THE BEGINNING OF CYCLE SIX, IF I'M READING THAT RIGHT, WE'RE DOWN TO 1403 COUNTS?
A. NO, MR. PASAHOW YOU'RE CONFUSING THE COUNTS WHICH ARE

OBSERVED AT THE END OF REACTION 5 INDICATED IN THE OBSERVED.

IT'S NOT THE ADJUSTED ONES, WE WOULD HAVE TO LOOK AT THE

OBSERVED ONES. WHICH IS, YES, RIGHT THERE.

Q. SO IT GOES FROM 3825 TO 1403?

A. YES.

Q. WHERE DID THEY GO?

A. BECAUSE YOU HAD 44 MORE ADDED VOLUME, YOU CAN SEE ADDED

VOLUME IS 4 SO WE'RE DILUTING BY ABOUT A FACTOR 3, SO THIS WOULD

MEAN NOW YOUR VOLUME IS A LOT LESS, YOUR COUNTS ARE GOING TO BE

LESS WHEN YOU TAKE OUT THE SAMPLE TO COUNT.

Q. DID YOU FIND THE SAME MATHEMATICAL CORRELATION BETWEEN THE

END OF 5 AND THE BEGINNING OF SIX THAT YOU FOUND FOR EACH OF THE

OTHER CYCLES?

A. REASONABLE. SOME VARIATION COUNTING OF COURSE AND THE

ACCURACY OF THE MEASUREMENT, BECAUSE AS I TOLD YOU BEFORE, YOU

WOULD HAVE TO TAKE OUT FIVE MICROLITERS AND DEPENDING ON YOUR

ERROR ACCURACY THERE WOULD BE SOME SLIGHT VARIATION.

Q. LET'S SEE. BETWEEN CYCLE ONE AND CYCLE 2 IT GOES FROM 900

TO 803?

A. RIGHT, YES.

Q. AND NEXT TIME IT GOES FROM 1754 TO 1405?

A. RIGHT, ABOUT A FACTOR, AS I'VE IN INDICATED, OF 1.6 OR

SOMETHING, 1.16 DILUTION FACTORS, THAT'S REASONABLY CLOSE.

Q. IN THE NEXT ONE IT GOES FROM 2767 TO THE TOTAL OF THESE TWO
BECAUSE HE DIVIDED IT IN HALF?

A. YES, RIGHT.

Q. AND HE GETS TO THE END OF THAT ONE AND FOR 5A HE GOES TWO
THROW 272,152?

A. YES.

Q. AND THEN HE GOES FROM 3825 TO 1403?

A. RIGHT.

Q. AND WHAT WAS YOUR DILUTION FACTOR THERE?

A. WELL, WHEN YOU GO FROM FIVE TO SIX YOU’RE ADDING 44 TO 17 SO
WITH A FACTOR THREE TO FOUR.

Q. A THREE AND A HALF TO EACH?

A. YES.

Q. THE HIGHEST ONE UP UNTIL THEN WAS WHEN SPLIT IT IN HALF?

A. YEAH.

Q. NOW, WHEN YOU FIGURED OUT WHAT HE ADDED IN NUMBER 6 DID YOU
HAVE TO AGAIN DECIDE WHETHER HE ADDED THESE COLD C’S ALONG WITH
THE HOT C’S?

A. YES, THEY’RE IN THE SAME COCKTAIL.

Q. YOU ASSUMED AGAIN HE HAD WRITTEN DOWN SOMETHING DIFFERENT
THAN WHAT ADDED?

A. NO, BECAUSE IT WAS FROM THE SAME WRITE OFF. I MEAN, I DID
NOT LOOK AT ANOTHER PART, I STILL WENT BACK TO THE SAME PART OF
THE PROTOCOL.

Q. YOU ASSUMED HE HAD ADDED THE COLD T’S EVEN THOUGH HE DIDN’T
WRITE DOWN THAT HE ADDED THEM?
A. C.

Q. I'm sorry, you assumed he added the cold C's even though he didn't write down --
A. The same specific activity.

Q. Now, you told us that Experiment 28 was a series of serial reactions I wrote down?
A. Yes.

Q. And you told us that three, four, five, six, seven, eight, nine were not serial reactions?
A. No, I said four, five, six, eight were not serial reactions.

Q. Three to nine?
A. That's correct.

Q. At the beginning of Experiment nine in the middle of this serial reaction Dr. Kleppe did a control of no heat; is that right?
A. That's right.

Q. So right in the middle of the serial reaction he put in his control?
A. No, because in that particular case, as I mentioned, frozen his reaction, so he was just checking at that particular time whether it was something unusual about freezing the reaction and using it again and -- showed there wasn't.

Q. That was a control?
A. That was part of the series also in that case, yes.

Q. One last thing... now, if I'm going to use the product of
ONE CYCLE AS TEMPLATE FOR ANOTHER CYCLE AS IS SHOWN IN THIS
CHART --
A. RIGHT.
Q. -- I HAVE TO HAVE GO FAR ENOUGH DOWN IN THIS CYCLE SO THAT I
INCLUDE THE SPOT WHERE MY TEMPLATE IS GOING TO ATTACH?
A. WHERE MY PRIMER IS GOING TO ATTACH.
Q. THANK YOU. WHERE MY PRIMER IS GOING TO ATTACH AND COME
BACK?
A. YES.
Q. THAT IS, YOU CAN USE THE PRODUCT OF ONE CYCLE AS TEMPLATE OF
THE NEXT CYCLE ONLY IF IT GOES CLOSE ENOUGH TO THE END TO
INCLUDE THE PRIMER BINDING CYCLE?
A. TO GO FAR ENOUGH SO YOU WOULD HAVE AT LEAST ENOUGH HYDROGEN
TO FORM A STABLE DUPEX.
Q. FOR THE TOP STRAND HERE WHAT'S CALLED DNA-V, HOW MANY OF THE
C'S DO I HAVE TO INCORPORATE IN ORDER TO INCLUDE THAT BINDING
CYCLE?
A. I DON'T FOLLOW YOUR REACTION. THE TOP STRAND . . .
Q. FOR THE TOP STRAND WHEN I AM EXTENDING THE TOP STRAND WITH
THE NONA, HOW MANY OF THE C'S THAT ARE GOING TO BE MADE HERE DO
I HAVE TO MAKE IN ORDER TO GET FAR ENOUGH DOWN SO THAT MY NEW
PRODUCT CAN BE USED IN THE NEXT CYCLE AS A TEMPLATE?
A. I WOULD SAY AT LEAST FOUR.
Q. SO ALL EXCEPT FOR THE LAST C?
A. BECAUSE WE ALREADY KNOW WORKS OUT THAT FAR.
Q. AND COMING BACK THE OTHER WAY WITH THE BOTTOM STRAND, HOW MANY OF THESE C’S DO I HAVE TO MAKE IN ORDER TO MAKE SURE I HAVE A BINDING SITE?

A. SIX. AGAIN, LEAVING OUT A FINAL C.

Q. LEAVE OUT THIS ONE?

A. YEAH.

Q. I HAVE ONE, TWO, THREE, FOUR . . . SO IF I GOT JUST TO THIS C I’D HAVE ENOUGH FOR A BINDING SITE?

A. NO, YOU ASKED ME ABOUT THE RADIOACTIVITY, WE CANNOT SEE THE OTHER ONES OBVIOUSLY.

Q. HAVE TO BE SOMEWHERE IN BETWEEN THESE TWO C’S?

A. I WOULD LIKE TO BE CLOSE TO THE FINAL C, BUT WE CANNOT FOLLOW THAT BY THE REACTION BECAUSE THOSE OTHER ONES ARE NOT RADIOACTIVE.

Q. NOW, DO YOU RECALL THAT DR. KLEPPE AND DR. KHORANA REPORTED THAT THE EXPERIMENTS THEY WERE DOING THAT THEY PUBLISHED WHEN THEY USED THE NONA WITH THE TOP STRAND THEY GOT 33 PERCENT INCORPORATION?

A. IS THIS THE --

Q. FIGURE 13.

A. THE SEPARATED STRANDS YOU’RE TALKING ABOUT?

Q. YES.

A. YES, RIGHT.

Q. AND DO YOU RECALL THAT THEY REPORTED WHEN THEY USED THE DECA WITH THE BOTTOM STRAND THEY REPORTED THAT THEY GOT 75 PERCENT?
A. RIGHT.

MR. PASAHOW: I HAVE NOTHING FURTHER, YOUR HONOR.

THE COURT: OKAY. I ASSUME THIS WITNESS CAN BE EXCUSED WITHOUT BEING SUBJECT TO BEING RECALLED?

MR. FIGG: YES, YOUR HONOR.

MR. PASAHOW: YES, YOUR HONOR.

THE COURT: HOW ABOUT THAT.

THE WITNESS: GO BACK TO CANADA.

THE COURT: YOU'RE WELCOME BACK ANYTIME, AT LEAST YOU WON'T HAVE TO COME NEXT TIME.

LADIES AND GENTLEMEN, AS YOU KNOW WE'VE GOT A LONG HIATUS. NOW, REMEMBER ALL OF THIS UNTIL WE COME BACK A WEEK FROM TODAY, SAME TIME, SAME PLACE, MONDAY MORNING AT 8:00 O'CLOCK. PLEASE FOLLOW THE INSTRUCTIONS ABOUT NOT DISCUSING THE MATTER INVOLVED IN THIS TRIAL OR IN ANY WAY FORMING OR EXPRESSING YOUR OPINION ABOUT THE MATTER AND WE'LL SEE YOU ON . . . WHAT DATE DOES THAT TURN OUT TO BE?

THE CLERK: 4TH.

THE COURT: FEBRUARY 4TH AT 8:00 O'CLOCK. IF YOU WOULD TAKE YOUR ENVELOPES AND YOUR BINDERS AND ALL YOUR MATERIALS RELATING TO THIS CASE AND PUT EVERYTHING IN THE JURY ROOM AND MS. MORIYAMA WILL TAKE CARE OF IT FOR YOU. THANK YOU.

(PROCEEDINGS HELD IN OPEN COURT, JURY NOT PRESENT:)

THE COURT: ARE THERE ANY MATTERS WE NEED TO TAKE UP NOW? DO YOU NEED TO TAKE THE MARTINELL MATTER UP BEFORE NEXT
MARTINELL WAS A MOTION, SO WE FILED OUR REPLY TO THAT AND FAXED A COPY LAST NIGHT TO YOU.

THE COURT: WELL, LAST NIGHT.

MR. FIGG: IN CASE YOU WERE HERE LAST NIGHT AND WANTED TO READ IT.

THE COURT: NOBODY TO TAKE IT OFF THE FAX MACHINE LAST NIGHT. HEAVEN KNOWS WHERE IT GOES, I HAVE NO IDEA.

WHAT MATTERS DO YOU NEED -- YOU LOOK AS IF YOU HAVE SOMETHING YOU WOULD LIKE TO RAISE?

MR. PASAHOW: AT SOME POINT I NEED TO MOVE TO ADMIT THE
EXHIBITS THAT WERE IDENTIFIED.

MR. FIGG: SO DO WE, AND WE ALSO LIKE TO MAKE AN OFFER OF PROOF.

THE COURT: WITH RESPECT TO THE EXHIBITS, WHY DON'T YOU GIVE ME YOUR NUMBERS FIRST SINCE MAYBE THERE NO PROBLEMS WITH THOSE.

MR. PASAHOW: I THINK THAT'S RIGHT. THEY'RE B-206; B-207; B-208; B-209; B-210; B-211; B-212; B-213; B-214; B-217A THROUGH B-217D; B-218; B-223; B-224; B-225; B-226; B-227 THROUGH B-237.

THE COURT: THAT'S ALL?

MR. PASAHOW: YES, THEY'RE ALL THESE LARGE CHARTS THAT WE USED.

MR. FIGG: YOUR HONOR,

THE COURT: ANY OBJECTION? LOST TRACK.

MR. FIGG: I COULD NOT EVEN FOLLOW ALONG LET ALONE UNDERSTAND WHICH EXHIBITS WE WERE TALKING ABOUT. AND ALSO SOME OF THESE WE HAVE NEVER SEEN BEFORE, AND AS A MATTER OF FACT MOST OF THEM WE'VE NEVER SEEN BEFORE.

WOULD IT BE PERMISSIBLE, AND PERHAPS COUNSEL WOULD CONSENT TO THIS, WE COULD TAKE A LOOK AT THEM OVER THE BREAK WE HAVE AND -- I DON'T THINK THERE'S GOING TO BE A PROBLEM WITH THEM.

THE COURT: FINE. THE RECORD SHOULD REFLECT THAT IS LEFT THEN AND ... TAKE CARE OF THAT AND DON'T LEAVE IT UNDONE.
YES, WHAT DO YOU HAVE? WHAT DOES YOUR OFFER PROOF
RELATE TO?

MR. FIGG: MAYBE I CAN DEAL WITH THAT FIRST, YOUR
HONOR. THE OFFER OF PROOF RELATES TO THE QUESTION THAT I PUT TO
DR. VAN DE SANDE ABOUT HIS UNDERSTANDING OF WHOSE IDEA IT WAS IN
THE KORANA LABORATORY TO PERFORM THESE REACTIONS.

IF PERMITTED TO TESTIFY WE BELIEVE DR. VAN DE SANDE
WOULD HAVE STATED WHEN HE JOINED THE KORANA LABORATORY DR.
KORANA DESCRIBED THIS MULTI-STEP AMPLIFICATION PROCESS THAT IS
NOW KNOWN AS PCR TO HIM AND BASED ON THESE DISCUSSIONS IT WAS
DOCTOR VAN DE SANDE’S UNDERSTANDING THAT DR. KORANA HAD
CONCEIVED OF THIS PROCESS PRIOR TO DR. KLEPPE’S AND DR. MOLINEUX
JOINING THE LABORATORY.

THE COURT: AND INDEED WITH THAT OFFER I WOULD HAVE
SUSTAINED THE OBJECTION. BUT THE OFFER IS ON THE RECORD.

MR. FIGG: THANK YOU, YOUR HONOR.

THE COURT: ARE THERE OTHER EXHIBITS THEN OR IS THAT
IT?

MR. FIGG: WE HAVE SOME OTHERS. MR. KURZ IS MORE
FAMILIAR WITH THESE EXHIBITS. WE’VE DONE A LITTLE INVENTORY
SINCE THIS IS BASICALLY THE END OF OUR CASE IN CHIEF, SO PERHAPS
I CAN LET HIM ADDRESS THIS.

THE COURT: HOW LONG A LIST IS THIS?

MR. KURZ: IT’S NOT VERY LONG, JUST A FEW.

THE COURT: OKAY.

MR. PASAHOW: THERE'S NO OBJECTION TO THAT, YOUR HONOR.

THE COURT: WHY DON'T WE JUST PROCEED, IF THERE'S AN OBJECTION NOTE IT. OTHERWISE, I'LL ASSUME THERE IS NONE.

MR. KURZ: A-157, A-169 --

MR. PASAHOW: AS TO A-157 WE CONTINUE TO OBJECT, YOUR HONOR. THAT'S THE TIME LINE.

MR. KURZ: THERE WERE TWO TIME LINES, ONE INVOLVED RE-EXAM, THE OTHER INVOLVED THE DEVELOPMENT, YOU OBJECT TO BOTH OF THOSE?

MR. PASAHOW: YES.

MR. KURZ: THE NEXT ONE IS A-169 WHICH IS THE UPDATED VAN DE SANDE CV.

MR. PASAHOW: NO OBJECTION.

MR. KURZ: A-126A WHICH IS THE UPDATED DE GRANDI CV.

MR. PASAHOW: NO OBJECTION.


MR. PASAHOW: THERE'S NO OBJECTION TO THAT.

MR. KURZ: A-173.

MR. PASAHOW: NO OBJECTION.

MR. KURZ: AND WE ALSO HAD A-148 WHICH THERE WAS -- WE'D LIKE TO AGAIN OFFER THAT INTO EVIDENCE. THAT WAS AGAIN THE TIME LINE OF THE RE-EXAMINATION.

WE'D ALSO LIKE TO CLARIFY A-67 AND A-67A THERE WAS SOME QUESTION WHETHER THOSE HAVE BEEN ADMITTED AND OUR REVIEW OF THE
TRANSCRIPT INDICATE THEY WERE ADMITTED INTO EVIDENCE.

MR. PASAHOW: THERE'S NO OBJECTION TO THEM IF THEY WERE

NOT ADMITTED.

THE COURT: IF THE RECORD DOESN'T REFLECT THE COURT'S

MINUTES DON'T REFLECT THEY'RE ADMITTED. ALL THE REST OF THE

DOCUMENTS YOU HAVE ENUMERATED ARE ADMITTED.

(PLAINTIFF'S EXHIBITS A-24, A-169,


A-67A RECEIVED IN EVIDENCE)

WHAT ABOUT THE SECOND TIME LINE, HE'S PROFFERING THE

ONE WITH RESPECT TO THE RE-EXAMINATION?

MR. LEWIS: THAT'S ONE WE DISCUSSED DURING MR. DE

GRANDI'S TESTIMONY.

THE COURT: WHAT ABOUT THE OTHER ONE, WHAT'S YOUR

OBJECTION?

MR. LEWIS: THE OTHER ONE CONTAINS SOME MATTER ABOUT

WHICH I DON'T BELIEVE THERE WAS ANY TESTIMONY AND I BELIEVE IT'S

MISLEADING. IT HAS AN ENTRY ABOUT A TERMINAL DISCLAIMER BEING

FILED TO OVERCOME OBVIOUSNESS WHICH WE DON'T AGREE WITH A FAIR

CHARACTERIZATION, AND IT'S IN GENERAL ON A CHART THAT HAS TO DO

WITH EVENTS IN THE SCIENCE.

THE COURT: WELL, LET'S DO THIS:

UNLESS YOU CAN CLEAN IT UP THE TIME LINE SO THAT BOTH

OF YOU CAN AGREE, IF YOU'RE GOING TO PERSISTS IN SEEKING TO HAVE

THEM ADMITTED AT LEAST BE ABLE TO SUPPORT THE ENTRIES AS HAVING

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SOME BASIS, IF NOT ANY TESTIMONY BURIED IN SOME OF THE DOCUMENTS
THAT HAVE BEEN ADMITTED.

MR. KURZ: WE LIKE TO RESERVE OUR RIGHT TO DO THAT.

THE COURT: OKAY. FINE. WHO ARE OUR WITNESSES GOING
TO BE ON ON THE FOURTH?

MR. PASAHOW: DOCTOR FALKINHAM AND DOCTOR HAMMILTON
SMITH.

THE COURT: DOCTOR FALKINHAM IS GOING TO START FIRST?

MR. FIGG: WE WERE INFORMED MR. RUDY ANDERSON WAS THE
NEXT WITNESS, YOUR HONOR.

MR. PASAHOW: WELL, IF WE WERE GOING TO HAVE A WITNESS
TODAY IT WOULD HAVE BEEN DOCTOR ANDERSON. SCHEDULES BEING WHAT
THEY ARE A WEEK FROM TODAY AND WITH THE STIPULATION I'M SAYING
THAT OUR WITNESSES ARE GOING TO BE DOCTOR FALKINHAM AND MR.
HAMMILTON SMITH.

MR. FIGG: YOUR HONOR, MR. PASAHOW STOOD UP HERE LAST
WEEK AND SAID IT WOULDN'T MAKE SENSE FOR MR. ANDERSON TO COME
OUT HERE ON MONDAY THEN HAVE TO COME BACK AGAIN A WEEK FROM
MONDAY. THERE WAS A CLEAR INDICATION HE WAS THEIR NEXT WITNESS.

THE COURT: IT'S NOT AS IF YOU DON'T HAVE A FEW DAYS TO
PREPARE.

MR. FIGG: I UNDERSTAND THAT. BUT OBVIOUSLY WE NEED TO
KNOW WHO THEIR NEXT WITNESSES ARE.

THE COURT: NOW YOU KNOW. THIS IS MORE NOTICE THAN YOU
ORDINARILY IF WE WERE CONVENING TOMORROW YOU WOULD NOT HAVE THE
ADVANTAGE. COME ON, GIVE ME A BREAK. I'VE GOT MORE IMPORTANT THINGS TO DO THEN HEAR YOU QUIBBLE ABOUT A WITNESS WHO ISN'T GOING TO TESTIFY FOR A WHOLE WEEK.

MR. FIGG: THERE'S ONE OTHER ITEM I DON'T KNOW IF WE CAN GET CLARIFICATION ON IT. DURING THE PRE-TRIAL CONFERENCE THERE WAS SOME INDICATION EITHER DR. ERLICH AND MR. ORNHARM (PHONETIC) WILL BE TESTIFYING BUT NOT BOTH, THAT AFFECTS REALLY THE WITNESS LIST I WONDER IF COUNSEL HAS ANY IDEA ABOUT THAT.

MR. PASAHOW: DR. ERLICH WILL TESTIFY.

THE COURT: HOW LONG WILL DOCTOR FALKINHAM BE?

MR. PASAHOW: ABOUT TWO TO THREE HOURS, DEPENDING ON THE CROSS-EXAMINATION.

THE COURT: IS THIS THE GENTLEMEN WITH THE VIDEO?

MR. PASAHOW: YES, YOUR HONOR.

THE COURT: THEN YOUR SECOND WITNESS?

MR. PASAHOW: DOCTOR HAMILTON SMITH.

THE COURT: HOW LONG WILL HE BE?

MR. PASAHOW: OUR DIRECT OF HIM WILL TAKE THE REST OF THAT DAY AND PROBABLY GO INTO THE NEXT DAY.

THE COURT: OKAY. NOT SURPRISING. THANK YOU. HAVE A GOOD WEEK AND WE'LL SEE YOU ON THE 4TH.

MR. FIGG: THANK YOU.

(The above matter adjourned at 1:15 P.M.)

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