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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

BEFORE THE HONORABLE MARILYN HALL PATEL, JUDGE

E.I. DU PONT DE NEMOURS & CO.,)
)
PLAINTIFF,)
)
VS.) NO. C 89-2860 MHP
)
CETUS CORPORATION, A DELAWARE)
CORPORATION,)
)
DEFENDANT.)
)

SAN FRANCISCO, CALIFORNIA
THURSDAY, FEBRUARY 7, 1991

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FOR PLAINTIFF:

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E.I. DU PONT DE NEMOURS & CO., INC.
LEGAL DEPARTMENT
WILMINGTON, DELAWARE 19898

BY: GEORGE A. FRANK, ESQ
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(APPEARANCES CONTINUED ON NEXT PAGE)

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I N D E X

THURSDAY, FEBRUARY 7, 1991 8:00 A.M.

(PROCEEDINGS HELD IN OPEN COURT, JURY PRESENT:)

MR. FIGG: GOOD MORNING, YOUR HONOR.

THE COURT: GOOD MORNING.

GOOD MORNING, LADIES AND GENTLEMEN.

I UNDERSTAND FROM THE REPORTERS THAT YOU TAKE THE PRIZE FOR THE ALL TIME LONGEST ANSWER, 11 AND A HALF PAGES. I DON'T KNOW WHICH ONE THAT WAS.

OKAY. READY TO PROCEED?

MR. FIGG: SURE.

KARY BANKS MULLIS, DEFENDANT'S WITNESS, PREVIOUSLY SWORN RESUMED

CROSS-EXAMINATION RESUMED

BY MR. FIGG:

Q. GOOD MORNING, DR. MULLIS.

A. GOOD MORNING, MR. FIGG.

Q. DR. MULLIS, I'D LIKE TO SHOW YOU A . . . A POSTER THAT WE PREPARED THAT HAS COPY OF A DOCUMENT THAT . . .

THE COURT: DOES THIS HAVE AN EXHIBIT NUMBER?

MR. FIGG: IT HASN'T BEEN MARKED.

THE COURT: IT'S ABOUT TO HAVE?

MR. FIGG: YES.

THE COURT: OKAY.

(PAUSE IN THE PROCEEDINGS)

THE CLERK: PLAINTIFF'S A-184 MARKED FOR IDENTIFICATION ONLY.

(PLAINTIFF'S EXHIBIT A-184 MARKED FOR IDENTIFICATION)

Q. (BY MR. FIGG) DR. MULLIS, YOU MAY HAVE TO COME DOWN HERE, BUT CAN YOU -- CAN YOU IDENTIFY THIS DOCUMENT?

A. IT LOOKS LIKE PROBABLY CAME OUT OF MY NOTEBOOK.

Q. OKAY. PERHAPS YOU'D LIKE TO STEP DOWN. I'M GOING TO ASK YOU SOME QUESTIONS ABOUT THIS DOCUMENT.

THIS IS A DIAGRAM THAT YOU PREPARED DESCRIBING A CERTAIN REACTION THAT YOU PLANNED TO CARRY OUT; IS THAT CORRECT?

A. YES, IT IS.

Q. AND THIS ILLUSTRATES, THIS PART OF THE DOCUMENT HERE ILLUSTRATES A PCR REACTION THAT YOU INTENDED TO PERFORM?

A. YES, IT DOES.

Q. AND THE REACTION BEGINS WITH A DOUBLE-STRANDED TEMPLATE THAT IS A 58 BASE PAIR REGION; IS THAT RIGHT?

A. YES. I SYNTHESIZED THAT 58 BASE PAIR PIECE OF DNA AS A MODEL FOR A SECTION OF THE BETA-GLOBIN GENE.

Q. THAT 58 BASE PAIR SECTION WAS SYNTHESIZED, AT LEAST PART OF IT WAS SYNTHESIZED USING YOUR OLIGONUCLEOTIDE SYNTHESIZER?

A. YES, IT WAS.

Q. YOU ALSO SYNTHESIZED THESE TWO PRIMERS; IS THAT CORRECT, JB04, AND JB03?

A. YES.

Q. AND THEY WERE SYNTHESIZED IN YOUR OLIGONUCLEOTIDE SYNTHESIZER?

A. I CAN'T RECALL WHETHER THEY WERE MADE ON THE MACHINE OR WHETHER THEY WERE HANSENS, THEY WERE PROBABLY MADE ON THE MACHINE.

Q. AND THE REACTION THAT'S ILLUSTRATED HERE FROM THE ARROW DOWN JUST ILLUSTRATES THE TYPICAL PCR REACTION; IS THAT RIGHT?

A. IT'S RATHER A TYPICAL -- ACTUALLY IT DOESN'T START WITH -- FROM A SEQUENCE, IT'S EMBEDDED IN ANOTHER SEQUENCE.

Q. WHAT I MEANT WAS, IT'S TYPICAL IN THAT YOU SHOWN THE TWO PRIMERS ANNEALED TO THE THREE-PRIME ENDS OF THE TEMPLATE STRANDS AND YOU HAVE ARROWS INDICATING THAT IN THE PCR REACTION THESE PRIMERS WOULD BE FILLED UP TO THE ENDS, IS THAT WHAT THAT INDICATES?

A. IT INDICATED THAT WAS -- YES, THAT'S WHAT IT INDICATES.

I WOULD CALL TO YOUR ATTENTION THAT NORMALLY IN THE FIRST CYCLE OF THE PCR REACTION THE PRIMERS DO NOT ANNEAL TO THE THREE-PRIMER ENDS OF THE TEMPLATE.

Q. BUT IN THIS ONE THEY DO?

A. IN THIS ONE MODEL REACTION, YES, THEY DO.

Q. SO HERE THE PRIMERS ARE LINED UP PRECISELY WITH THE THREE-PRIME ENDS OF THE TEMPLATE MODULE?

A. THAT'S CORRECT.

Q. OKAY. DO YOU STILL HAVE YOUR '202 PATENT UP THERE, DR. MULLIS?

A. YES, I DO.

Q. MAYBE YOU COULD TAKE A LOOK AT THAT. I'D LIKE TO DIRECT YOUR ATTENTION TO A CERTAIN PORTION OF IT.

A. I'M GLAD TO HEAR THAT YOU DECIDED IT IS MINE.

Q. WELL, I USE THE TERM ADVISEDLY. I THINK WE UNDERSTAND IT'S CETUS', THOUGH, DON'T WE?

A. WELL, I THINK IT'S MINE.

Q. DOCTOR, WOULD YOU LOOK AT COLUMN FIVE OF YOUR PATENT, LINES 47 THROUGH 48.

Q. DO YOU SEE THE SENTENCE THERE THAT SAYS:

"THE SPECIFIC NUCLEIC ACID SEQUENCE TO BE AMPLIFIED MAY BE ONLY A FRACTION OF A LARGER MOLECULE OR CAN BE PRESENT INITIALLY AS A DISCRETE MOLECULE, SO THAT THE SPECIFIC SEQUENCE CONSTITUTES THE ENTIRE NUCLEIC ACID."

I'M JUST ASKING IF YOU --

A. YES, I SEE THAT.

Q. NOW --

A. IT GENERALLY TRUE THAT IT BEGINS AS A FRACTION OF A LARGER MOLECULE AND DURING THE COURSE OF THE AMPLIFICATION IT BECOMES A DISCRETE MOLECULE.

Q. YES. ACTUALLY, IN THE THIRD ROUND OF -- THIRD CYCLE IT BECOMES A DISCRETE MOLECULE?

A. THAT'S RIGHT.

Q. AND BUT THIS LANGUAGE HERE SAYS IT CAN BE PRESENT INITIALLY

AS A DISCRETE MOLECULE, SO THAT THE SPECIFIC SEQUENCE CONSTITUTES THE ENTIRE NUCLEIC ACID.

AM I CORRECT THAT THIS ILLUSTRATION ON EXHIBIT A-184 IS AN EXAMPLE OF A SITUATION WHERE IT IS A DISCRETE MOLECULE SUCH THAT THE SPECIFIC SEQUENCE CONSTITUTES THE ENTIRE NUCLEIC ACID?

A. YES, THAT'S CORRECT.

Q. THAT'S WHAT THAT LANGUAGE MEANS?

A. THAT LANGUAGE IS ACTUALLY THE WAY IT IS. BECAUSE THE CLAIMS OF THE PATENT ARE WRITTEN IN TERMS OF PAIRS OF CYCLES. THEY CAN BE IN THE BEGINNING OF THE REACTION, IN WHICH CASE THE TARGET IS NOT GENERALLY DISCREET MOLECULE.

THEY COULD BE LATER IN THE REACTION WHEN, IN FACT, MOST OF THE TARGET IS A DISCRETE MOLECULE BECAUSE OF THE NATURE OF THE REACTION.

Q. IT CAN BE EITHER WAY, IS THAT WHAT YOU'RE SAYING?

A. I'M SAYING THE CLAIMS ARE WRITTEN IN SORT OF AN ELEGANT FASHION AND THE ELEGANCE IS IN THE FACT THAT THE SAME WORDS CAN DESCRIBE SLIGHTLY DIFFERENT SITUATION.

Q. BUT THE LANGUAGE YOU JUST READ FROM THE PATENT, WHICH SAYS IT CAN BE PRESENT INITIALLY AS A DISCRETE MOLECULE, MEANS THAT INITIALLY AT THE VERY BEGINNING OF THE CLAIM, OF THE PROCESS DESCRIBED IN THE CLAIM, THIS NUCLEIC ACID THAT'S BEING AMPLIFIED CAN BE A DISCRETE MOLECULE?

A. THAT'S TRUE. IT MEANS IT CAN. IT CERTAINLY INCLUDES THAT.

Q. AND SO THIS REACTION ON YOUR DOCUMENT THAT WE'VE MARKED AS

EXHIBIT A-184, IF CARRIED OUT UNDER THE CONDITIONS SPECIFIED IN YOUR CLAIMS TO AMPLIFY THIS 58 BASE PAIR FRAGMENT, WOULD BE COVERED BY CLAIM 1?

A. IF IT IS CARRIED OUT UNDER THE CONDITIONS SPECIFIED BY THE CLAIMS, THEN IN FACT IT FALLS UNDER THE CLAIMS.

Q. RIGHT. NOW, DOCTOR, THE DUPLEX THAT YOU'RE AMPLIFYING HERE IS 58 BASE PAIRS, I THINK WE AGREED ON THAT?

A. YES. AS A MODEL FOR THE 58 BASE PAIR FRAGMENT THAT WE AMPLIFIED OUT OF THE BETA-GLOBIN GENE.

Q. AND THE PRIMERS COME TO WITHIN ONE NUCLEOTIDE OF ACTUALLY OVERLAPPING ON THE TEMPLATE, SO THE PRIMERS, THE COMBINED TOTAL NUMBER OF NUCLEOTIDES IN THE PRIMERS WOULD BE 57 BASE PAIRS, RIGHT?

A. YES. THAT ONE BASE PAIR IN THE MIDDLE IS THE ONE WHICH WE WERE TRYING TO DIAGNOSE.

Q. SO AFTER YOU GO THROUGH ONE CYCLE OF AMPLIFICATION, IF IT -- YOU WERE A HUNDRED PERCENT EFFICIENT, YOU WOULD START WITH 58 BASE PAIRS, YOU WOULD NOW HAVE TWO COPIES OF THAT, CORRECT?

A. AS DRAWN THERE -- THERE IS NO, IN FACT -- I HAVE NOT DRAWN ON THERE A CYCLE OF AMPLIFICATION OF A DUPLEX. I'VE INDICATED THAT THAT WOULD BE THE NEXT STEP.

AND IF, IN FACT, YOU WERE TO ASSUME THAT I -- THAT -- I MEAN, TO EXTEND BOTH OF THOSE PRIMERS ON THE TWO STRANDS OF THE DUPLEX, AND THAT I MEAN TO HAVE IT HAPPEN ONE HUNDRED PERCENT WHICH I CERTAINLY WOULD HAVE, THEN I WOULD HAVE ENDED UP WITH

FOUR STRANDS.

Q. IN THE FIRST CYCLE YOU ENDED UP WITH TWO STRANDS, RIGHT? YOU DOUBLE THIS INITIAL --

A. DEPENDS WHAT WE'RE TALKING ABOUT AS THE FIRST CYCLE. AS THIS DIAGRAM IS DRAWN I STARTED OUT WITH ONE PRIMER AND ONE SINGLE-STRANDED TEMPLATE AND I WOULDN'T CALL THAT ACTUALLY A PCR CYCLE.

Q. RIGHT. I UNDERSTAND. I UNDERSTAND THAT POINT.

SO LET'S MAKE SURE THIS IS CLEAR. WHAT YOU'RE DEPICTING IN THIS PART OF THE REACTION, IS YOU ARE SIMPLY MAKING THIS DOUBLE-STRANDED TEMPLATE BY EXTENDED ONE OF THE PRIMERS 01 OF THE TEMPLATES?

A. THAT'S CORRECT.

Q. SO WE'RE PERHAPS TALKING ABOUT THE SAME THING, BUT USING DIFFERENT TERMINOLOGY.

IF WE TAKE THIS AS THE BEGINNING OF THE PCR REACTION THEN IN THE NEXT CYCLE YOU WOULD HAVE TWO COPIES OF THIS 58 BASE PAIR DUPLEX IF IT WAS HUNDRED PERCENT EFFICIENT?

A. I DON'T WANT TO SEEM PICKY HERE, BUT I SOMETIMES WORRY ABOUT IT WHEN YOU SEEM TO STRESS A FACT THAT I DON'T BELIEVE IS TRUE, THEN YOU REPEAT THE SAME FACT.

TO ME THE FIRST ARROW, THAT WHICH IS GOING FROM A SINGLE-STRANDED TEMPLATE PRIMED BY A SINGLE PRIMER, TO WHAT WILL BECOME A DUPLEX, IS NOT IN MY OPINION WHAT YOU WOULD CALL A FIRST CYCLE.

YOU SEEM TO WANT TO GO BACK TO -- NOW WE'RE TALKING ABOUT THE NEXT CYCLE, WHEN REALLY WE'RE TALKING ABOUT THE FIRST CYCLE PCR.

Q. I ACCEPT THAT.

A. LET'S BE CLEAR.

Q. SO THE FIRST CYCLE WILL BE THE CYCLE THAT'S ILLUSTRATED HERE BY THESE ARROWS INDICATING YOU'RE EXTENDING OUT, IS THAT WHAT YOU'RE SAYING?

A. YES.

Q. THE ONLY POINT I'M TRYING TO MAKE IS THAT AFTER YOU'VE COMPLETE THAT YOU WILL HAVE DOUBLED THE AMOUNT OF THAT 58 BASE PAIR FRAGMENT?

A. THAT IS TRUE.

Q. SO YOU STARTED OUT WITH 58 BASE PAIRS AND NOW YOU HAVE A HUNDRED AND 16 BASE PAIRS IN THESE TWO NEW MOLECULES THAT YOU'VE CREATED?

A. IF YOU WANT TO COUNT THE BASE PAIRS AS INDIVIDUAL ENTITIES, WHICH I THINK IS AGREEABLE WITH ME, THEN I HAVE A HUNDRED 16 OR WHATEVER.

Q. RIGHT. AND IF YOU --

A. IT IS A FUNNY WAY TO DESCRIBE IT BECAUSE THEY AREN'T ACTUALLY SINGLE ENTITIES AS THEY'RE DRAWN ON THERE. THE -- I MEAN, THAT REPRESENTS MANY MILLIONS OF MOLECULES AND IF YOU WANT TO TALK ABOUT HOW MANY BASE PAIRS WE ENDED UP HAVING, IT SEEMS SILLY TO SAY A HUNDRED 16 BASE PAIRS.

Q. BUT THIS IS THE WAY YOU'VE ILLUSTRATED HERE, YOU ILLUSTRATED ONE MOLECULE WHICH IS TYPICAL AND EVERYONE UNDERSTANDS YOU'RE ILLUSTRATING SOMETHING THAT'S OCCURRING MANY TIMES OVER IN THE SAME REACTION TUBE?

A. OKAY. I WOULD PREFER TO TWO 58 BASE PAIR MOLECULES.

Q. BUT IF YOU HAVE TWO OF THEM THERE ARE TOTAL OF A HUNDRED 16 BASE PAIRS IN THEM?

A. MR. FIGG, MY ANSWER IS THAT WE WOULD HAVE TWO 58 BASE PAIRS MOLECULES. IT WOULD BE EMBARRASSMENT TO ME AS A PROFESSIONAL CHEMIST TO TALK ABOUT IT AS A HUNDRED AND 16 BASE PAIRS. THAT'S NOT THE WAY THAT OLIGONUCLEOTIDE OR DNA CHEMISTS WOULD TALK TO EACH OTHER.

116 BASE PAIRS DENOTES THE IDEA 116 BASE PAIRS LONG. IT DOES NOT DENOTE THE IDEA OF TWO 58 BASE PAIR MOLECULES. IT'S SORT OF A -- IT MAKES THE WHOLE THING QUITE VAGUE.

Q. WELL, IF YOU'LL BEAR WITH ME, DOCTOR, I'M NOT DISPUTING THE FACT THAT YOU GO FROM ONE MOLECULE TO TWO, SO THERE ARE TWO 58 BASE PAIR MOLECULES, BUT THE SUM OF THE NUMBER OF BASE PAIRS IN THOSE TWO MOLECULES WILL NOW BE A HUNDRED 16, SIMPLE ARITHMETIC, RIGHT?

A. IT'S OKAY -- IF YOU WANT TO TALK ABOUT IT THAT WAY, BUT I'M NOT GOING TO SAY IT.

Q. YOU DON'T DISAGREE WITH ME, THOUGH, THAT MY ARITHMETIC IS CORRECT?

A. I DON'T UNDERSTAND WHERE YOU'RE GOING AND I SUSPECT THAT

IT'S SOMETHING STRANGE. WHY DON'T YOU TALK ABOUT IT THE WAY IT WOULD NORMALLY BE TALKED ABOUT? WHY ARE YOU NOW THIS MORNING TALKING ABOUT TWO TIMES 58 IS A HUNDRED 16, SO LET'S TALK ABOUT 116 BASE PAIRS.

Q. DOCTOR, I'D LIKE FOR YOU TO ANSWER MY QUESTION. PERHAPS YOU DON'T UNDERSTAND THE REASON I'M ASKING IT, BUT I THINK I'M ENTITLED TO AN ANSWER.

A. WELL, I THINK I'VE GIVEN YOU ONE.

Q. ALL RIGHT. IF YOU DO ANOTHER CYCLE YOU AGAIN DOUBLE THE AMOUNT OF THE 58 BASE PAIRS DUPLEX AND NOW YOU WOULD HAVE FOUR OF THESE 58 BASE PAIR DUPLEXES?

A. IF YOU WERE TO DO ANOTHER CYCLE AND IT WERE TO WORK, YES, YOU WOULD.

Q. AND IF YOU ADDED UP ALL OF THE BASE PAIRS IN THOSE FOUR YOU NOW HAVE 232?

A. YES, THAT IS CORRECT.

Q. NOW, THE PRIMERS THAT YOU'RE STARTING OUT WITH, IF YOU PUT IN EXACTLY THE AMOUNT OF PRIMERS THAT ARE CONSUMED IN THE REACTION IN THE FIRST CYCLE YOU'RE GOING TO -- YOU'RE GOING TO PUT IN 57 BASE PAIRS TOTAL OF PRIMER, RIGHT?

A. ABSOLUTELY NOT. THAT IS SUCH A RIDICULOUS WAY TO TALK ABOUT IT. THE PRIMER DOESN'T COME IN BASE PAIRS. THE PRIMER COMES IN SINGLE NUCLEOTIDES STUCK TOGETHER. IT'S A SINGLE-STRANDED MOLECULE.

WHY DO YOU NOW GO TO THIS CURRENCY OF BASE PAIRS TO

DESCRIBE WHAT NO ONE ELSE DESCRIBES IN DNA CHEMISTRY LIKE THAT. WHY DO YOU FEEL THE NEED TO START DESCRIBING THINGS THAT HAVE PERFECTLY LOGICAL AND REASONABLE EXPLANATIONS FOR THE TERMS THAT ARE USED IN TERMS NO ONE CAN -- WHY DISTORT EVERYTHING INTO BASE PAIRS.

OBVIOUSLY A PRIMER DOESN'T HAVE ANY BASE PAIRS IN IT. IT WAS NUCLEOTIDES. DO YOU WANT TO TALK ABOUT IT IN NUCLEOTIDES?

MR. FIGG: YOUR HONOR -- OKAY. LET ME REPHRASE THE QUESTION, DR. MULLIS.

Q. YOU'RE PUTTING IN THESE PRIMERS, YOU'RE PUTTING IN A TOTAL OF 57 NUCLEOTIDES IN TWO MOLECULES, IF YOU ADDED UP ALL THE NUCLEOTIDES IN THOSE TWO MOLECULES THERE ARE 57; IS THAT RIGHT?

A. ACTUALLY, NOT IN THE PRIMERS. WELL, OKAY, THERE'S -- THERE'S -- THERE ARE 57 NUCLEOTIDES COMING IN AS PRIMERS INTO THE REACTION AS DEPICTED THERE. OKAY.

Q. OKAY.

A. IT SEEMS TO ME YOU'RE TRYING TO CONFUSE SOMETHING. IT'S EARLY IN THE MORNING FOR ME. I DON'T SEE THE NEED FOR THIS.

Q. I HOPE I'M NOT TRYING TO CONFUSE THINGS.

THE POINT IS SIMPLY THIS, DOCTOR, IF YOU -- IF YOU USED A LARGE EXCESS OF THESE TWO PRIMERS IN THIS REACTION THAT YOU'VE ILLUSTRATED HERE, YOU WOULD ACTUALLY BE GENERATING LESS NEW DNA THAN YOU WERE PUTTING IN IN THE FORM OF SYNTHETIC DNA, ISN'T THAT CORRECT?

A. THAT IS CORRECT.
Q. SO THE NET SYNTHESIS OF DNA, IF YOU PUT IN A LARGE EXCESS OF PRIMERS, THE NET SYNTHESIS OF DNA WOULD ACTUALLY BE A NEGATIVE NUMBER?
A. THE NET SYNTHESIS BEING DEFINED AS WHAT?
Q. BEING DEFINED AS THE AMOUNT OF DNA PRODUCT THAT YOU'RE SYNTHESIZING COMPARED TO THE AMOUNT OF SYNTHETIC DNA THAT YOU'RE PUTTING IN THE REACTION.
A. YOU MEAN, THE AMOUNT OF PRODUCT MINUS THE AMOUNT OF SYNTHETIC DNA?
Q. THE AMOUNT OF PRODUCT THAT YOU'RE GETTING OUT OF THE REACTION COMPARED TO THE AMOUNT OF SYNTHETIC DNA THAT YOU'RE PUTTING INTO THE REACTION.
A. COMPARED TO --
Q. YES.
A. ARE YOU -- YOU WANT ME TO ASSUME THAT NET IS REFERRING TO A RATIO?
Q. NO. THE AMOUNT OF PRODUCT DNA THAT YOU'RE GETTING OUT OF THE REACTION COMPARED TO THE AMOUNT OF SYNTHETIC DNA YOU'RE PUTTING IN; IN OTHER WORDS, YOU ARE ACTUALLY PUTTING IN MORE SYNTHETIC DNA THAN YOU'RE GETTING OUT IN THE FORM OF PRODUCT, ISN'T THAT CORRECT?
A. BUT THEN -- I MEAN, IF YOU WANT TO TALK ABOUT NET SYNTHESIS --
Q. CAN YOU ANSWER THAT QUESTION?

A. I'M PUTTING IN --

MR. PASAHOW: EXCUSE ME, YOUR HONOR, I THINK MR. FIGG CUTOFF THE WITNESS' ANSWER.

THE COURT: CAN YOU ANSWER THE QUESTION AS IT'S FRAMED?

THE WITNESS: I'M NOT TRYING TO BE DIFFICULT. I FEEL THAT THE QUESTION IS BEING -- IT'S BEING FRAMED IN A WAY THAT DOESN'T HAVE ANY MEANING TO ME.

IT'S HARD TO ANSWER THE QUESTION WHEN HE SAYS NET. TO ME NET MEANS SOMETHING LESS, SOMETHING THE NET SYNTHESIS WOULD BE THAT AMOUNT WHICH WAS SYNTHESIZED MINUS THAT WHICH WAS DESYNTHESIZED, SOMETHING ON THAT.

IT'S NOT USUALLY USED, THE NET, IN MY USAGE OF THE WORD IS NOT A COMPARISON OF TWO THINGS, IT'S A DIFFERENCE BETWEEN SOMETHING THAT YOU -- WHAT YOU GET BACK MINUS WHAT YOU STARTED WITH.

Q. (BY MR. FIGG) DOCTOR, I DON'T THINK MY LAST QUESTION USED THE WORD NECESSARY.

A. THAT WHOLE THING IS CONFUSING TO ME.

Q. IF I'M CORRECT IF YOU USE A LARGE EXCESS OF PRIMERS IN THIS REACTION THAT YOU'VE ILLUSTRATED HERE, THAT YOU WILL GET LESS DNA OUT, LESS OF THIS 58 BASE PAIR PRODUCT IN TOTAL IN TERMS OF THE TOTAL NUCLEOTIDES, YOU WILL GET LESS OF THAT OUT THAN YOU PUT IN TO THE REACTION TO BEGIN WITH?

A. OKAY. BUT YOU'RE SAYING THAT USING THEM IS SOMETHING -- PUTTING THEM IN, RIGHT?

Q. RIGHT?
A. I WOULD SAY THEY GET USED WHEN THEY ARE TRANSFORMED INTO SOMETHING ELSE. JUST PUTTING THEM IN THE REACTION IS NOT THE SAME THING AS USING THEM. THEY'RE STILL THERE. THEY'RE NOT GOING AWAY. IF THEY'RE NOT GOING AWAY THEN WHY SHOULD YOU SUBTRACT THEM FROM THE AMOUNT OF DNA THAT'S BEING PRODUCED TO GET SOME NET SYNTHESIS. THEY'RE STILL THERE.
Q. THEY'RE STILL THERE, BUT THEY ARE IN THE FORM OF THIS PRODUCT THAT YOU'RE SEEKING TO MAKE?
A. BUT THEY'RE IN THE FORM THEY WERE IN WHEN I PUT THEM IN THE REACTION IN THE FIRST PLACE.
Q. BUT YOUR GOAL IS TO MAKE THIS PRODUCT, IS IT NOT?
A. YES, IT IS.
Q. AND MY POINT SIMPLY IS THIS: AND I'D LIKE FOR TO YOU TRY TO ANSWER MY QUESTION.

ISN'T IT TRUE THAT THE PRODUCT, THE AMOUNT OF PRODUCT THAT YOU GET OUT OF THAT REACTION, IF YOU USE A LARGE EXCESS OF THESE PRIMERS, THE AMOUNT OF PRODUCT THAT YOU GET OUT OF THAT REACTION IS GOING TO BE LESS THAN THE AMOUNT OF DNA THAT YOU INITIALLY PUT IN THE TUBE?
A. YES.
Q. THANK YOU.

DOCTOR, WHAT IS -- WHAT IS THE MATERIAL THAT'S CALLED TRIS OR TRIS HCL THAT I'VE SEEN IT INDICATED AS SOMETIMES?
A. IT'S A BUFFER REAGENT. IT'S A BASE THAT CAN BE PRONATED OR

NOT DEPENDING ON THE PH'S. IT'S A SPONGE FOR PROTONS.

Q. IT'S ONE OF THESE THINGS THAT WE'VE BEEN CALLING A BUFFER?

A. YES.

Q. AND IT'S USED FOR CONTROLLING ACIDITY OF A REACTION?

A. YES, PH OF A REACTION WHICH IS --

Q. YEAH. YOU HAVE USED TRIS OR TRIS HCL IN YOUR PCR REACTIONS, HAVEN'T YOU?

A. YES, I HAVE.

Q. THAT'S WORKED SUCCESSFULLY FOR YOU?

A. YES, IT HAS.

Q. AND WHAT IS MAGNESIUM ACETATE?

A. THE BUSINESS END THAT WOULD BE THE MAGNESIUM, MAGNESIUM IS A DIVALENT, D-I-V-A-L-E-N-T, MEANING IT HAS A CHARGE PLUS TWO ON IT. IT'S A DIVALENT ATOM WHICH IS NECESSARY FOR THE POLYMERASE ACTIVITY AND ALSO IT IS BOUND TO THE NUCLEOTIDES.

Q. AN ACID TO THE ACETATE PORTION OF IT IS JUST THE OTHER PART OF THE MAGNESIUM SALT?

A. YES, IT IS A NECESSARY PART OF IT TO KEEP THE MAGNESIUM ATOMS IN THE BOTTLE.

Q. YOU'VE SOMETIMES USED MAGNESIUM CHLORIDE AS THE SOURCE OF THE MAGNESIUM ION FOR YOUR PCR REACTIONS I BELIEVE; IS THAT RIGHT?

A. YES.

Q. HAVE YOU ALSO USED MAGNESIUM ACETATE?

A. YES, I'VE USED BOTH.

Q. MAGNESIUM ACETATE WORKS PERFECTLY OKAY IN PCR REACTIONS?

A. YES.

Q. AND SODIUM CHLORIDE IS JUST COMMON TABLE SALT; IS THAT RIGHT?

A. YES, IT IS.

Q. YOU'VE USED SODIUM CHLORIDE IN YOUR PCR REACTIONS FOR ESTABLISHING THE SALT CONCENTRATION?

A. YES, I HAVE.

Q. AND DTT IS THIS COMPOUND IS CALLED DITHIOTHREITOL?

A. YES, IT IS.

Q. YOU'VE USED THAT IN YOUR PCR REACTIONS FOR STABILIZING THE POLYMERASE ENZYME?

A. YES, I HAVE.

Q. THAT'S A COMMON MATERIAL TO INCLUDE IN REACTIONS THAT INVOLVE DNA POLYMERASE; IS THAT RIGHT?

A. YES, IT IS.

Q. SODIUM CHLORIDE IS A COMMON MATERIAL TO USE IN REACTIONS THAT INVOLVE DNA POLYMERASE?

A. YES, WE ALREADY WENT OVER THAT.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) DR. MULLIS, REFERRING BACK TO YOUR CLAIM 1 HERE, AM I CORRECT THAT THIS CLAIM DOESN'T REQUIRE THE PRESENCE OF GENOMIC DNA AS THE STARTING MATERIAL FOR AMPLIFICATION?

A. YOU'RE CORRECT, MR. FIGG.

Q. AND THIS CLAIM DOESN'T REQUIRE THAT THE STARTING MATERIAL BE

A DNA THAT'S ASSOCIATED WITH A GENTIC DISEASE?

A. CERTAINLY NOT.

Q. OR WITH AN INFECTION AGENT OF ANY KIND?

A. OBVIOUSLY NOT.

Q. IT CAN BE ANY KIND OF DNA?

A. IT COULD BE.

Q. DOCTOR, DO YOU AGREE WITH ME, THAT THIS CLAIM IS BROADER IN ITS SCOPE THAN ANY OF THE PROCESSES DESCRIBED IN THE EXAMPLES OF THE '202 PATENT, EVEN EXAMPLE 1?

A. THE EXAMPLES ARE GIVEN AS EXAMPLES. AND THE CLAIM IS WRITTEN IN BROADER TERMS TRYING TO DESCRIBE PRETTY MUCH THE WHOLE -- THE WHOLE PROCESS. IT'S NOT -- I MEAN, WHY SHOULDN'T IT BE? OF COURSE, IT IS IS THE ANSWER. OF COURSE, IT IS.

Q. IT'S BROADER THAN ANY OF THE EXAMPLES?

A. OF COURSE, IT IS, MR. FIGG.

Q. DOCTOR, YOU WERE IN THE COURTROOM WHEN DOCTOR MOLINEUX WAS DESCRIBING SOME OF HIS WORK, IS THAT -- AM I CORRECT ON THAT?

A. YES, I WAS HERE.

Q. AND DID YOU HEAR DR. MOLINEUX DESCRIBE HIS WORK WITH THE DNA THAT HE CALLED DNA-I?

A. I HEARD HIM GIVE HIS RECOLLECTION OF HIS WORK.

Q. AND YOUR FAMILIAR WITH WHAT DNA-I IS DR. MOLINEUX WAS DESCRIBING IT?

A. I -- I KNOW WHERE TO FIND THAT SEQUENCE IN THE LITERATURE. I COULDN'T WRITE IT DOWN FROM MEMORY.

Q. YOU HAVEN'T MEMORIZED IT I UNDERSTAND, BUT IT WAS A PIECE OF DNA ABOUT 16 NUCLEOTIDES IN LENGTH. DO YOU RECALL THAT?

A. I ACTUALLY DON'T REMEMBER WHETHER IT WAS 16 OR NOT. IF YOU HAVE A PICTURE OF IT, UNLESS THERE'S NO NEED FOR ME TO KNOW SPECIFICALLY ABOUT IT.

Q. I DON'T THINK THAT THAT IS AN ESSENTIAL FACT.

BUT AM I CORRECT THAT IF YOU USE DNA-I AS THE STARTING MATERIAL IN HERE AND YOU CARRIED OUT THE STEPS OF THIS REACTION AS DESCRIBED IN THIS CLAIM AND YOU ACHIEVED SUCCESSFUL TARGET DEPENDENT AMPLIFICATION, THAT THAT REACTION WOULD BE COVERED BY THIS CLAIM?

A. WHEN YOU SAY "ACHIEVED SUCCESSFUL TARGET DEPENDENT AMPLIFICATION," ARE YOU DESCRIBING A PROCESS IN WHICH THE PRODUCTS OF THE EXTENSION OF THE PRIMERS IN ONE CYCLE BECOME THE TEMPLATES FOR THE EXTENSION OF THOSE PRIMERS IN THE NEXT CYCLE?

Q. THAT'S SET FORTH IN THE CLAIM, SO, YES, I AM INCLUDING THAT.

A. OKAY. I JUST WANT TO MAKE SURE THAT'S WHAT YOU MEANT BY AMPLIFICATION.

Q. SO THE ANSWER, AM I CORRECT, YOU DID THAT WITH DNA-I IT WOULD BE COVERED BY THIS CLAIM?

A. IF, IN FACT, IT WORKED IT WOULD BE COVERED BY THAT CLAIM.

Q. AND I THINK YOU WERE ALSO IN THE COURTROOM WHEN DOCTOR VAN DE SANDE WAS DESCRIBING THE EXPERIMENTS DR. KLEPPE PERFORMED BACK IN 1969?

A. DR. VAN DE SANDE WAS -- YES, I WAS PRESENT.

Q. AND DO YOU RECALL DR. VAN DE SANDE DESCRIBING SOME EXPERIMENTS IN WHICH DR. KLEPPE WAS WORKING WITH THE DNA CALLED DNA-II?

A. I RECALL THAT. AGAIN, I DON'T RECALL THE SPECIFICS.

Q. RIGHT. YOU DON'T RECALL THE SEQUENCE AND NEITHER DO I, BUT DNA-II WAS SOMETHING ROUGHLY 29 OR 30 BASES LONG, DO YOU RECALL THAT?

A. IT JIVES MY MEMORY.

Q. I THINK THAT'S SUFFICIENT.

A. I CAN'T PICTURE THOSE MOLECULES EXACTLY.

Q. MY QUESTION IS SIMPLY THIS:

IF YOU STARTED WITH DNA-II, YOU CARRIED OUT THE STEPS DESCRIBED IN THIS CLAIM AND SUCCESSFULLY ACHIEVED TARGET DEPENDENT AMPLIFICATION, AM I CORRECT THAT THAT PROCESS OR THAT REACTION WOULD BE COVERED BY THIS CLAIM?

A. THE ANSWER IS, YES, AND IN CASE YOU'RE PLANNING TO GO THROUGH MORE, I'VE ALREADY ANSWERED THE QUESTION. ANY DNA THAT YOU START WITH IT DOESN'T HAVE TO -- IT DOESN'T HAVE TO BE A DISEASE DNA.

ANY DNA THAT YOU START WITH IF YOU GO THROUGH THE PROCESS DESCRIBED BY THOSE CLAIMS AND YOU SUCCESSFULLY AMPLIFY IT IN A WAY THAT IS DESCRIBED BY THOSE CLAIMS THEN, IN FACT, YOU ARE DOING SOMETHING BY DEFINITION THAT IS DESCRIBED BY THOSE CLAIMS.

Q. OKAY. THANK YOU, DOCTOR.

DOCTOR, THERE'S BEEN SOME TESTIMONY CONCERNING THE USE OF PRIMERS WHOSE SEQUENCES OVERLAP. AM I CORRECT THAT YOUR CLAIM DOESN'T PRECLUDE THE USE OF OVERLAPPING PRIMERS PROVIDED THAT THE REACTION WORKS AS SET FORTH IN THE CLAIM?

A. YOU'RE CORRECT.

Q. AND, IN FACT, WOULD YOU LOOK AT EXAMPLE 1 OF YOUR '202 PATENT THAT I THINK YOU STILL HAVE BEFORE YOU.

A. I STILL HAVE THAT IN MEMORY ACTUALLY.

Q. DO YOU RECALL THAT THE PRIMERS THAT WERE USED IN EXAMPLE -- EXCUSE ME, LET ME GET THIS MARKED.

I'VE PLACED ON THE EASEL A POSTER ENTITLED '202 PATENT EXAMPLES. WE'D LIKE TO HAVE THAT MARKED FOR IDENTIFICATION, PLEASE.

THE CLERK: PLAINTIFFS A-185 MARKED FOR IDENTIFICATION ONLY.

(PLAINTIFF'S EXHIBIT A-185 MARKED FOR IDENTIFICATION)

Q. (BY MR. FIGG) DR. MULLIS, AM I --

MR. PASAHOW: EXCUSE ME.

MR. FIGG: I'M SORRY.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) DOCTOR, AM I CORRECT THAT THE PRIMERS THAT ARE USED IN EXAMPLE 1 ACTUALLY HAVE SEQUENCES AT OR CLOSE TO THEIR THREE-PRIME ENDS WHICH ARE COMPLEMENTRY TO EACH OTHER, AND AT LEAST ON PAPER CAN BE DRAWN AS FORMING A COMPLEX LIKE THE ONE

ILLUSTRATED HERE?

A. I BELIEVE THAT THEY DO. I ASSUME THAT YOU COPIED THE SEQUENCES CORRECTLY.

Q. WE TRIED TO. ALTHOUGH, IT'S EASY TO MAKE MISTAKES ON THOSE THINGS.

IF YOU HAVE THE PATENT I'LL READ THE SEQUENCES TO YOU.

A. OKAY. I'VE READ IT. THAT LOOKS CORRECT TO ME.

Q. OKAY. AND IN EXAMPLE 4 OF YOUR PATENT PRIMERS WERE USED WHICH HAVE SEQUENCES RIGHT AT THE END THAT, IN FACT, ARE COMPLEMENTRY AND ON PAPER CAN BE DRAWN AS FORMING THIS KIND OF A COMPLEX?

A. I THINK THAT'S FAIR TO SAY.

Q. AM I CORRECT THAT THERE IS NO DISCUSSION IN YOUR '202 PATENT OR IN THE '195 THAT -- THAT INDICATES THAT PRIMERS WITH STRUCTURES LIKE THIS SHOULD BE AVOIDED?

A. THERE -- THERE IS NO DISCUSSION, AS FAR AS I KNOW IN THERE, THAT SAYS THOSE SHOULD BE AVOIDED. THERE'S CERTAINLY NO DISCUSSION IN THERE THAT RECOMMENDS THAT YOU TRY THOSE EXCEPT FOR THE EXAMPLES AS THEY ARE SET OUT.

Q. YEAH. THE PATENT JUST DOESN'T SAY ANYTHING AT ALL ABOUT OVERLAPPING PRIMERS?

A. IT ACTUALLY DOES. IT QUOTES A PAPER BY ROSSI, ET AL. IN THE BODY OF THE PAPER IN WHICH OVERLAPPING PRIMERS ARE USED IN A PROCESS WHICH IS DESCRIBED IN HERE AS BEING ANOTHER WAY THAT YOU CAN MAKE DNA SYNTHETICALLY.

IT CERTAINLY SETS THAT PROCESS APART FROM PCR BY CITING IT IN THE SPECIFICATION AND SAYING HERE IS ANOTHER WAY THAT ROSSI ET AL. HAVE SHOWN THAT YOU CAN MAKE A DOUBLE-STRANDED DNA.

YOU CAN MAKE A DOUBLE-STRANDED DNA BY TAKING TWO OLIGONUCLEOTIDES THAT ARE COMPLEMENTRY TO EACH OTHER ON THE THREE-PRIME ENDS AND EXTENDING THEM ON EACH OTHER, IT DESCRIBES THAT IN ROSSI ET AL. AND SETS IT APART FROM THE TEACHINGS OF THE '202.

Q. IT WAS KNOWN IN THE PRIOR ART FROM THE ROSSI PAPER IF THERE'S SUFFICIENT COMPLIMENTARITY THE THREE PRIME ENDS SUCH THAT YOU CAN FORM A COMPLEX BETWEEN THEM YOU CAN INDEED EXTEND THEM OUT?

A. IT WAS POINTED OUT IN THE PATENT. ROSSI ET AL. DID NOT DESCRIBE THE SITUATION LIKE YOU HAVE THERE FROM EXAMPLE 1 WHERE THE THREE PRIMED BASE ITSELF IS NOT BASE PAIRED, BUT ROSSI WAS INTENTIONALLY TRYING TO EXTEND PRIMERS ON EACH OTHER AND THERE HE WOULD HAVE GOTTEN THE BASE PAIRS EXACTLY RIGHT.

I CERTAINLY WAS NOT INTENDING TO EXTEND MY PRIMERS IN EXAMPLE 1 AS IS CLEARLY POINTED OUT BY THE PATENT.

Q. SURE, I WASN'T SUGGESTING THAT YOU WERE.

IF THIS KIND OF A COMPLEX ACTUALLY DID FORM, THIS WOULD BE CAPABLE OF EXTENDING OUT FROM THE G, THE THREE PRIMED G ON THE LOWER PRIMER ON THIS WAY, WOULDN'T IT?

A. GIVEN DNA POLYMERASE AND THE APPROPRIATE NUCLEOTIDES.

Q. AND IF YOU WERE USING CONDITIONS WHERE THE POLYMERASE

EXONUCLEASE ACTIVITY WOULD CLIP THIS G OFF THEN IF THIS KIND OF A COMPLEX FORMED THIS WOULD EXTEND OUT IN THIS DIRECTION, RIGHT?

A. THAT IS CORRECT. CERTAINLY WOULD NOT BE PCR, NEITHER WOULD IT BE UNDER THE CLAIM.

Q. RIGHT.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) DOCTOR, THESE PRIMERS THAT WE WERE TALKING ABOUT EARLIER -- I'M SORRY, LET ME GET THIS ONE MARKED TOO.

WE MADE A POSTER OF PAGE 116 OF DR. MULLIS' NOTEBOOK.

(PAUSE IN THE PROCEEDINGS)

THE CLERK: PLAINTIFF'S B-186 MARKED FOR IDENTIFICATION ONLY.

(PLAINTIFF'S EXHIBIT B-186 MARKED FOR IDENTIFICATION)

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) THIS IS COPIED FROM YOUR NOTEBOOK NUMBER 1365, DR. MULLIS. DO YOU RECOGNIZE THIS PAGE?

A. YES, I DO.

Q. OKAY. WHAT YOU'VE ILLUSTRATED ON HERE ARE SOME OF THE PRIMERS THAT WE'VE BEEN TALKING ABOUT EARLIER; IS THAT RIGHT?

NAMELY, ONE CALLED JB04 AND ANOTHER ONE CALLED JB03.

A. YES.

Q. AND THOSE PRIMERS WERE ILLUSTRATED IN CONNECTION WITH THE EXPERIMENT WITH THE 58 BASE PAIR FRAGMENT THAT WE TALKED ABOUT EARLIER THIS MORNING, THIS FRAGMENT HERE (INDICATING).

THESE ARE THE SAME PRIMERS --

A. YES, THEY ARE.

Q. -- THAT ARE ILLUSTRATED HERE (INDICATING)?

THEY ARE ALSO, I BELIEVE, THE SAME PRIMERS THAT ARE USED IN EXAMPLE TEN OF THE '202 PATENT?

THAT WAS ACTUALLY AN EXPERIMENT WHERE YOU USED TWO SETS OF PRIMERS SEQUENTIALLY AND I BELIEVE THIS REPRESENTS THE SECOND SET.

A. CORRECT, THERE'S THE SECOND SET. THAT WAS THE NESTED PRIMER EXPERIMENT IN WHICH THE SECOND SET OF PRIMERS CAME IN AND AMPLIFIED A 58 BASE PAIR FRAGMENT OUT OF A HUNDRED TEN BASE PAIR FRAGMENT THAT HAD BEEN AMPLIFIED BEFORE BY ANOTHER SET OF PRIMERS.

Q. OKAY. WHAT -- AM I CORRECT THAT WHAT IS ILLUSTRATED ON THIS PAGE OF YOUR NOTEBOOK IS THE SECONDARY STRUCTURE THAT THESE PRIMERS ARE CAPABLE OF ASSUMING?

A. THAT'S CORRECT. WHAT I WAS TRYING TO DO THERE, MR. FIGG, I WAS TRYING TO FIGURE OUT WHY IN CERTAIN REACTIONS WHERE I WAS USING THOSE PRIMERS WITHOUT TEMPLATE THAT I WAS -- I WAS NONETHELESS GETTING SOMETHING THAT LOOKED A BIT LIKE THE 58 BASE PAIR PRODUCT THAT I WAS FORMING. THAT I WAS EXPECTING TO FIND OUT IN THE PRESENCE OF TEMPLATE.

NOW, AS IT TURNED OUT THE EXPLANATION FOR THAT LAY IN CONTAMINATION. I WAS STARTIN TO GET VERY HIGH AGAIN -- OR HIGHLY EFFICIENT AMPLIFICATIONS AND IT TURNED OUT THAT HAVING

BEGUN TO DO THAT I WAS STARTING TO PRODUCE 58 BASE PAIR FRAGMENTS ALL OVER THE PLACE IN THE LABORATORY.

SO THAT IT BECAME VERY DIFFICULT TO FIND A SOLUTION TO START A REACTION IN THAT WOULD NOT AFTER TEN OR 20 CYCLES PRODUCE WHAT LOOKED TO BE PART OF THE AMPLIFICATION PRODUCT OF A BETA-GLOBIN TEMPLATE.

THE SOLUTION TO WHY I WAS ALSO GETTING A PRODUCT MADE EVEN IF I DIDN'T PUT INTENTIONALLY A TEMPLATE IN TURNED OUT TO BE CONTAMINATION AND I LEARNED HOW TO KEEP MY SOLUTIONS MUCH CLEANER. I BEGAN TO APPRECIATE FOR THE FIRST TIME THAT WHEN YOU WERE DOING PCR IN YOUR LAB THAT IT WAS ALMOST LIKE GROWING, LIKE CLONING BACTERIAL SEQUENCES.

THINGS -- I HAD TO START TREATING MY SOLUTIONS LIKE THEY WERE INFECTIOUS. I HAD TO START WEARING GLOVES, I NEVER WANTED TO DO THAT BEFORE. I STARTED HAVING TO TREAT EVERYTHING VERY CAREFULLY. IT'S A PROBLEM THAT HAS INTENSIFIED AS PCR HAS DEVELOPED TO WHERE IT CAN AMPLIFY SMALLER AND SMALLER AMOUNTS OF SOMETHING TO LARGER AND LARGER AMOUNTS.

THAT SET OF PRIMERS I SUSPECTED THAT MAY BE THAT SET OF PRIMERS WAS RESPONSIBLE FOR THE ARTIFACTS AND THAT'S WHY I DID THESE CALCULATIONS TO SEE WHAT SORT OF STRUCTURE THEY COULD POSSIBLY FORM.

IT TURNED OUT THAT DIMMER DOWN IN THE LOWER RIGHT-HAND CORNER DID ACCOUNT FOR A BAND ON A GEL THAT I WAS CONTINUALLY GETTING EVEN IF I HAD VERY HIGHLY PURIFIED JB03 IT ALWAYS HAD

TWO BANDS AND I NEVER HAD FIGURED THAT OUT UNTIL I DID THIS CALCULATION AND SAID, AH, THAT'S IT, IT CAN FORM A CERTAIN AMOUNT OF THAT DIMMER.

NOW, THAT DIMMER DIDN'T LOOK EXACTLY LIKE THE 58 BASE PAIR PRODUCT AND I INVESTIGATED FURTHER AND DISCOVERED THAT THE 58 BASE PAIR PRODUCT THAT I WAS GETTING AND WHAT I THOUGHT WERE REACTIONS THAT DID NOT HAVE TEMPLATE IN IT. THAT 58 BASE PAIR PRODUCT REALLY WAS COMING FROM TEMPLATE.

THE TEMPLATE WAS INADVERTENTLY ADDING CONTAMINATION IT TURNED OUT TO HAVE THAT358 PAIR FRAGMENT ALL OVER MY HANDS, ALL OVER THE SOLUTIONS BECAUSE WE WERE MAKING SO MUCH OF IT WE WERE NOT REALLY YET USE TO THE IDEA WE COULD YET MAKE HUGE AMOUNTS OF THINGS.

WE WERE GOING ON HAVE TO START BEING CAREFUL IF WE WANTED TO HAVE ZERO CONTROLS AGAIN. THAT WAS VERY INTERESTING EPIC IN THE DEVELOPMENT OF MY APPRECIATION OF THE POWER OF PCR.

Q. YOU DIDN'T INTENTIONALLY DESIGN THESE PRIMERS TO HAVE THESE STRUCTURES THAT YOU'VE DRAWN ON YOUR NOTEBOOK HERE; IS THAT RIGHT?

A. NATURE DESIGNED THOSE PRIMERS BY HAVING THEM ABOUT, FLANKING THE SITE IN THE MIDDLE OF THE BETA-GLOBIN GENE I WAS INTERESTED IN.

Q. YOU SELECTED THAT RIGHT AS THE POINT OF -- FOR THE SEQUENCE OF THE PRIMERS, BUT YOU DIDN'T SELECT THAT SITE BECAUSE THE PRIMERS WOULD FORM THE STRUCTURE, THAT WAS JUST A NECESSARY

CONSEQUENCE OF THE SEQUENCE YOU WERE AMPLIFYING?

A. NATURE SELECTED THAT SITE TO HAVE MUTATION BECAUSE SICKLE CELL ANEMIA I SIMPLY MADE THE APPROPRIATE PRIMERS USING THIS SEQUENCE THAT NATURE HAD PROVIDED FLANKING THAT SITE. I DIDN'T SELECT ANY OF THAT SITE.

Q. YOU DIDN'T HAVE THIS STRUCTURE IN MIND WHEN YOU INITIALLY PREPARED THE PRIMERS?

A. NO, I HAD THAT STRUCTURE IN MIND ON WHAT I THINK IS 8/16/84 WHEN I DID THOSE CALCULATIONS.

Q. SO WHAT YOU'VE FOUND WAS THAT THESE STRUCTURES WERE NOT ACCOUNTABLE FOR THE POTENTIAL PROBLEMS THAT YOU WERE SEEING IN YOUR AMPLIFICATIONS?

A. THEY WERE NOT ACCOUNTABLE FOR THE FACTUAL PRODUCTION OF THE 58 BASE PAIR FRAGMENT.

Q. RIGHT.

A. THEY WERE ACCOUNTABLE FOR CERTAIN THINGS THAT I HAD SEEN ON THE GELS, THAT STRUCTURE IN THE LOWER RIGHT-HAND CORNER, I HAD SEEN QUITE OFTEN. I DIDN'T KNOW WHAT IT WAS.

I KNEW THERE WAS ALWAYS A SPOT ON THE GEL THAT HAD JB03 THAT I COULDN'T ACCOUNT FOR AFTER MAKING THAT CALCULATION. I STARTED BEING ABLE -- I WAS QUITE PLEASED WITH MYSELF NOW I COULD FIGURE OUT WHAT THAT WAS.

Q. THIS STRUCTURE AT THE TOP, AT LEAST AS DRAWN ON PAPER, THEORETICALLY COULD BE EXTENDED FROM THIS THREE-PRIMED END THAT IS FOLDED BACK UPON ITSELF, IS THAT RIGHT?

THAT WAS THE REASON YOU WERE INVESTIGATING THIS?

A. WELL, THAT WAS ONE OF THE -- THAT WAS ONE OF THE POSSIBLE STRUCTURES THAT COULD HAVE HAPPENED. AND I HAD TO LOOK AT THAT AND SAY, COULD THIS THING MAKE A 58 BASE PAIR FRAGMENT OR SOMETHING THAT WOULD FOOL ME TO THINKING IT WAS A 58 BASE PAIR FRAGMENT?

THE ANSWER TO THE QUESTION WAS, NO, IT COULDN'T. IT WOULD MAKE SOMETHING, BUT WOULD NOT LOOK LIKE A 58 BASE PAIR FRAGEMENT ON A POLYMER GEL AND IT COULDN'T CLEAR WITH THE RIGHT ENZYMES.

THERE WERE A LOT OF CONSIDERATIONS TO TAKE INTO MIND AND I STUDIED THE WHOLE SITUATION IN A VERY CAREFUL WAY. NONE OF THOSE STRUCTURES REALLY TURNED OUT TO BE THE SOLUTION TO THE PROBLEM WHICH WAS WHY AM I GETTING A 58 BASE PAIR FRAGMENT WHEN I DON'T EVEN PUT ANY DNA IN THERE.

AND THE SOLUTION TURNED OUT TO BE I'M ACCIDENTALLY PUTTING DNA IN THERE. I FINALLY FIGURED THAT OUT. THOSE STRUCTURES REALLY HAD NOTHING DO WITH THE SOLUTION.

Q. I UNDERSTAND THAT. THESE STRUCTURES THAT YOU'VE DRAWN ON HERE DID NOT SIGNIFICANTLY INTERFERE WITH YOUR REACTION AT ALL?

A. NOT IN THE CONDITIONS THAT I PERFORMED IT. THEY MAYBE COULD HAVE INTERFERED WITH IT UNDER SOME OTHER CONDITIONS, BUT UNDER THE CONDITIONS I PERFORMED THE REACTION, IT TURNED OUT THE REACTION WORKED FINE DESPITE ALL THOSE STRUCTURES.

Q. DR. MULLIS, WHEN YOU WERE ANSWERING SOME OF MR. PASAHOW'S

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QUESTIONS I RECALL SOME TESTIMONY CONCERNING WORK THAT WAS GOING ON DOCTOR ERLICH'S LAB AND I THINK IN COLLABORATION WITH YOURSELF AND MR. SAIKI ON COMBINING THE PCR TECHNIQUE WITH ANOTHER TECHNIQUE CALLED OR, DO YOU RECALL THAT SUBJECT WAS DISCUSSED?

A. YES.

Q. AND I BELIEVE YOU INDICATED THAT THE WORK CONTINUED FOR ABOUT NINE MONTHS BEFORE YOU FELT THAT YOU WERE GETTING REPRODUCIBLE RESULTS USING THE COMBINATION OF THOSE TWO TECHNIQUES?

A. WE -- ACTUALLY MANY POINTS DURING THAT COLLABORATION WERE GETTING REPRODUCIBLE RESULTS. WE WOULD SOMETIMES HAVE REPRODUCIBLE RESULTS FOR A MONTH OR TWO, THEN WE SUDDENLY RAN INTO THE SAME PROBLEM THAT I WAS RUNNING INTO IN THE LAB. WHICH WAS, SUDDENLY EVERY TUBE WE COME UP WITH WHAT LOOKED TO BE THE AMPLIFICATION PRODUCT OF THE BETA-GLOBIN GENE OR SOMETHING LIKE THAT AND WE WOULDN'T UNDERSTAND WHY CAN'T WE GET NEGATIVE CONTROLS AGAIN. AND WE REALLY -- WE HAD TO FINALLY DEAL WITH THE IMMENSE PROBLEMS OF CONTAMINATION THAT YOU HAVE WHEN YOU'RE DOING 100,000 OR A MILLION-FOLD AMPLIFICATIONS.

IT'S LIKE YOU CAN'T BELIEVE HOW SMALL A FRACTION OF SOMETHING THAT A MILLIONTH OF SOMETHING IS. YOU FINALLY HAVE TO START BELIEVING IT AND REALIZE WHEN YOU OPEN A TUBE IN A LAB LITTLE DROPLETS OF LIQUID COME FLOATING OUT IN THE AIR AND SOME OF THEM LAND IN YOUR LABORATORY COAT, SOME OF THEM LAND IN YOUR

FINGERS, THEN YOU'RE DOING ANOTHER EXPERIMENT THE NEXT DAY YOU THINK YOU'RE NOT PUTTING ANY TARGET DNA IN THE TUBES SUDDENLY EVERY ONE OF THE TUBES COMES OUT CONTAINING THE TARGET.

THAT WAS ONE OF THE SERIOUS PROBLEMS AFTER WE GOT THE PCR TO REALLY WORK AND OR WAS WORKING WE SUDDENLY WE CONTAMINATED OUR ENTIRE LABORATORY BASE ON PCR PRODUCT, IT WOULD SUDDENLY COME UP COMPLETELY AMOK.

I THINK WE HAD THAT PROBLEM OVER AND OVER AGAIN AND WE FINALLY DEVELOPED METHODS, IN FACT, TO GUARD AGAINST THAT. BUT IT TOOK US A LONG TIME.

Q. THAT WAS ABOUT, I THINK YOU TOLD MR. PASAHOW, THAT WAS AROUND MIDSUMMER OF 1985?

I'M NOT HOLDING YOU TO THE EXACT DATE BUT ROUGHLY THAT'S THE DATE WE'RE TALKING ABOUT?

A. WE'RE NOT. I WAS TALKING ABOUT AN ONGOING PROCESS THAT HAS GOTTEN WORSE AND WORSE. THE BETTER PCR GETS THE MORE YOU HAVE TO GUARD AGAINST THIS CONTINUED PROBLEM OF CONTAMINATION.

WE WOULD HAVE IT SOMETIMES FOR -- SOMETIMES WE GO FOR A MONTH OR TWO. AT THE VERY BEGINNING WE WENT FOR A LONG TIME WITHOUT EVER HAVING IT BECAUSE OUR AMPLIFICATIONS WEREN'T SO EFFICIENT.

ONCE THEY GOT EFFICIENT SUDDENLY WE WERE WORKING ALONG A COUPLE OF MONTHS EVERYTHING WOULD BE DOING RIGHT SUDDENLY WE COULDN'T GET ANY NEGATIVE CONTROLS. SO WE HAD TO GO BACK AND FIGURE OUT WHAT'S HAPPENING HERE. ARE WE REALLY GETTING

SPECIFIC AMPLIFICATION. IF SO WHY DO WE GET AMPLIFICATION OUT OF A CELL OF DNA THAT'S NOT SUPPOSE TO HAVE ANY BETA-GLOBIN IN IT AT ALL. WE THEN HAVE TO SOLVE THAT PROBLEM.

IT WASN'T SOMETHING THAT JUST HAPPENED ONE DAY, YOU'RE TRYING TO PUT A DATE ON IT. YOU'RE SAYING EVERYTHING WAS PERFECT AS OF JUNE 1985.

Q. DR. MULLIS, ALL I WAS TRYING TO DO IS SEE IF I UNDERSTOOD WHAT YOU TOLD MR. PASAHOW. LET ME ASK THIS QUESTION:

THE OR TECHNIQUE IS NOT AMPLIFICATION, THAT'S A DETECTION TECHNIQUE, RIGHT?

A. I KNOW WHAT YOU'RE TALKING ABOUT. I REMEMBER WHAT I WAS TALKING TO MR. PASAHOW ABOUT.

Q. I'VE ASKED A DIFFERENT QUESTION NOW, IF YOU'D ANSWER THAT.

A. THE OR TECHNIQUE IS A DETECTION.

Q. OKAY. AND IT'S A DETECTION TECHNIQUE THAT INVOLVES A RADIOACTIVELY LABELED PROBE AND THEN INVOLVES SOME STEPS OF ANNEALING THAT PROBE AND ACHEIVING IT JUST AS A GENERAL DESCRIPTION; IS THAT CORRECT?

A. YES.

Q. WOULD YOU LOOK AT THE '202 PATENT THE CLAIM SECTION. AM I CORRECT THAT CLAIMS 16 THROUGH 18 ARE THE CLAIMS OF THAT PATENT THAT ARE SPECIFICALLY DIRECTED TO THE USE OF OR IN COMBINATION WITH PCR?

A. 16 THROUGH 18 OF THE '202?

Q. YES. I'M SORRY, I MISSPOKE, THE '195, I APOLOGIZE.

A. YES, THAT'S WHAT THOSE ARE REFERRING TO.
Q. AND DO YOU UNDERSTAND THAT THOSE CLAIMS ARE NOT EVEN BEING CHALLENGED BY DU PONT IN THIS LITIGATION?
A. I THINK YOU HAVE A HARDER TIME CHALLENGING THOSE THEN YOU'RE ASKING ME TO HAVE CHALLENGING THIS ONE.
Q. THE ANSWER IS YES, RIGHT?
A. YES.
Q. DOCTOR, REFERRING TO THE '195 CLAIM 1 OF THAT PATENT . . . DEFINES AN AMPLIFICATION PROCEDURE FOLLOWED BY A DETECTION PROCEDURE, IS THAT A FAIR CHARACTERIZATION OF IT?
A. THAT'S FAIR.
Q. AND THE PREAMBLE OF THE CLAIM ON STEPS A THROUGH C DESCRIBE THE AMPLIFICATION PROCEDURE EXACTLY AS SET FORTH IN THE '202 PATENT?
A. I BELIEVE IT'S EXACTLY THE SAME WORDING.
Q. OKAY. AND STEPS D AND E DEFINE THE DETECTION STEP WHICH INVOLVES TAKING ONE OF THESE RADIOACTIVELY LABELED PROBES THAT WE'VE BEEN TALKING ABOUT AND DETERMINING WHETHER OR NOT THAT PROBE WILL HYBRIDIZE OR STICK TO DNA THAT HAS BEEN AMPLIFIED?
IS THAT A FAIR CHARACTERIZATION OF THAT?
A. I THINK SO.
Q. NOW, JUST AS THE CLAIM 1 OF THE '202 PATENT, CLAIM 1 OF THE '195 ALSO DESCRIBES TWO CYCLES OF AMPLIFICATION?
A. YES.
Q. AND THERE'S ANOTHER CLAIM IN THE '195 THAT ADDS ONE

ADDITIONAL CYCLE FOR A TOTAL OF THREE; IS THAT RIGHT?

A. YES. I MIGHT POINT OUT TO YOU THE PRECISE WORDING IN THAT CLAIM, WHERE IT SAYS THE CLAIM IS REFERRING TO A PROCESS WHICH COMPRISES TWO CYCLES.

Q. RIGHT.

A. THAT DOES NOT ELIMINATE A PROCESS WHICH HAS OTHER THINGS IN IT. IN FACT, IT DOESN'T ELIMINATE A PROCESS WHICH HAS 50 CYCLES IN IT. YOU KEEP COMING BACK TO THAT POINT.

THE REASON IT IS WRITTEN AS TWO CYCLES IS BECAUSE FOR THE PROCESS TO REALLY WORK IT HAS TO INVOLVE TWO CYCLES. IT HAS TO HAVE THE COMPONENT THAT THE EXTENDED PRIMERS FROM ONE CYCLE ARE PRIMED BY THE OTHER PRIMERS IN THE NEXT CYCLE.

THAT'S WHY IT'S WRITTEN THAT WAY. IT SEEMS TO ME THAT YOU'VE MADE MUCH MORE THAN YOU SHOULD HAVE OF THE FACT THAT IT TALKS ABOUT TWO CYCLES. IT'S A PROCESS WHICH COMPRISES --

Q. COMPRISES IS THE WAY YOU UNDERSTAND IT, IS THAT IT INVOLVES AT LEAST TWO CYCLES?

A. YES.

Q. OKAY. SO IF I DO THIS REACTION AND I DO TWO CYCLES I'M COVERED BY THIS CLAIM?

A. YES, YOU ARE.

Q. UNLESS YOU DO THEM WRONG.

Q. WELL, I PROBABLY WOULD IF I DID THEM.

A. THAT'S WHAT I WAS THINKING OF.

Q. AND JUST AS THE '202 PATENT WOULD COVER A DISCREET DNA

MOLECULE SIMILAR TO THE ONE THAT WE DISCUSSED IN CONNECTION WITH EXHIBIT A-184, YOU COULD START WITH THAT KIND OF A DISCRETE DNA MOLECULE IN CLAIM 1 OF THE '195?

A. IT'S THE SAME WORDING.

Q. NOW, DOCTOR, WE HAD DISCUSSED YESTERDAY A TECHNIQUE CALLED SOUTHERN BLOTTING, AND I BELIEVE THAT YOU AGREED THAT SOUTHERN BLOTTING IS A DETECTION TECHNIQUE THAT WOULD BE ENCOMPASSED BY WHAT'S SET FORTH IN STEPS D AND E OF CLAIM 1?

A. IF SOUTHERN BLOTTING WERE PERFORMED -- A PCR AMPLIFICATION PRODUCT I BELIEVE THAT, IN FACT, IT WOULD FALL WITHIN THOSE CLAIMS.

Q. RIGHT. AND IN EARLY 1984 SOUTHERN BLOTTING WAS A STANDARD BIOCHEMICAL TECHNIQUE?

A. IN SOME LABORATORIES?

Q. IT WAS USED WIDELY IN MOLECULAR BIOLOGY LABORATORIES, ISN'T THAT CORRECT?

A. THAT IS CORRECT.

Q. AND, IN FACT, PROBABLY EVERYONE THAT WORKED ON THE SAME FLOOR THAT YOU DID AT CETUS WOULD HAVE BEEN AWARE THAT YOU COULD USE A SOUTHERN BLOT TO ANALYZE THE PRODUCT OF A PCR AMPLIFICATION, ISN'T THAT CORRECT?

A. NO, THAT'S NOT CORRECT. THE JANITORS WOULD PROBABLY USE A SOUTHERN BLOT FOR CLEANING UP THE SPILLS.

Q. ALL THE SCIENTISTS WOULD HAVE BEEN AWARE OF THAT?

A. YES, MR. FIGG.

Q. IN FACT, DR. MULLIS, YOU CONSIDERED IT OBVIOUS TO COMBINE A PROBING TECHNIQUE SUCH AS SOUTHERN BLOTTING WITH THE AMPLIFICATION TECHNIQUE DESCRIBED IN THE '195 AND THE '202 PATENTS, ISN'T THAT CORRECT?

A. I DID, I THINK I TOLD YOU THAT BEFORE.

(PAUSE IN THE PROCEEDINGS)

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

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) DR. MULLIS, DO YOU RECALL THAT YOU'RE NAMED AS THE PATENTEE ON THE PATENT FOR LABELING OLIGONUCLEOTIDES SUCH THAT THEY CAN BE USED AS HYBRIDIZATION PROBES?

A. YES, I THINK SO.

Q. AND THAT PATENT THAT'S . . . I'VE PLACED ON THE OVERHEAD PROJECTOR HERE THE FIRST PAGE OF U.S. PATENT 4,582,789, IS THAT THE PATENT THAT YOU RECALL YOU'RE NAMED ON AS AN INVENTOR?

A. YES.

Q. AND THIS PATENT DESCRIBES SPECIFIC WAY OF LABELING PROBES SO THAT THEY CAN BE USED TO DETECT DNA SEQUENCES IN MIXTURES?

A. YES, I THINK SO.

Q. AND THE PROBES THAT ARE MADE IN THIS, BY THE PROCEDURE DESCRIBED IN THIS PATENT, WOULD BE PROBES THAT COULD BE USED IN THE STEPS D AND C OF CLAIM 1 OF THE '195; IS THAT CORRECT?

A. I THINK THAT IT WOULD PROBABLY -- I'M NOT TERRIBLY FAMILIAR WITH THE PATENT THAT YOU'RE NOW DISCUSSING. IT IS ONE WHERE I HAD THE ORIGINAL IDEA AND SOME OTHER PEOPLE WENT -- TOOK IT

AHEAD AND DID ALL THE WORK AND BY THE TIME THEY GOT TO WRITING THE PATENT I WAS NOT TOO MUCH INVOLVED WITH THAT.

SO I HAVEN'T REALLY STUDIED THOSE CLAIMS TO KNOW WHETHER IT INCLUDES ALL THE NUCLEOTIDE PROBES OR ALL THE DNA. I WOULD ASSUME IT HAD BEEN WRITTEN THAT WAY.

Q. OKAY. LET ME SHOW YOU A PRINTED COPY OF THE PATENT, DR. MULLIS, THAT WE'VE HAD MARKED AS A-102.

DO YOU RECOGNIZE THAT AS THE PATENT THAT WE'RE TALKING ABOUT?

A. THIS IS THE PATENT THAT WE'RE TALKING ABOUT.

Q. YEAH. NOW, DO YOU SEE THAT THIS PATENT WAS BASED ON AN ORIGINAL PATENT APPLICATION THAT WAS FILED ON MARCH 21ST, 1984?

A. YES, I SEE THAT.

Q. IT WAS REFILED AGAIN LATER IN 1984 AND ULTIMATELY ISSUED INTO THE PATENT THAT WE'VE ILLUSTRATED?

A. YES.

Q. IN THE BACKGROUND SECTION OF THIS PATENT THERE'S A STATEMENT OF SORT OF THE STATE OF THE ART IN CONNECTION WITH USING LABELED HYBRIDIZATION PROBES, DO YOU SEE THAT IN COLUMN ONE?

A. WHAT LINE?

Q. WELL, I THINK IT BEGINS AROUND LINE 20.

A. YES. I SEE THAT STATEMENT.

Q. I'M SORRY.

A. I SEE THAT STATEMENT.

Q. IT BASICALLY IS SAYING THAT:

"IT IS OFTEN USEFUL TO HAVE INDICATOR PROBES WHICH ALLOW THE USER TO DETECT, MONITOR, LOCALIZE OR ISOLATE NUCLEIC ACID PRESENT IN ANY AMOUNT."

DO YOU SEE THAT?

A. IT IS OFTEN USEFUL, YES.

Q. AND IT GOES ONTO SAY:

"THAT SUCH PROBES HAVE BEEN USED TO DETECT THE PRESENCE OF GENES CODING FOR ANTIGENS RESPONSIBLE FOR THE GRAFT REJECTION, AND SO FORTH."

AND JUST LISTS AS PART OF THE STATE OF THE ART VARIOUS USES OF LABEL PROBES FOR HYBRIDIZATION?

A. YES.

Q. DO YOU AGREE THAT THIS IS AN ACCURATE, PERHAPS SOMEWHAT ABBREVIATED SUMMARY, OF THE STATE OF THE ART USING DETECTION PROBES IN EARLY 1984?

A. YES. I THINK THAT'S WHAT THE INTENTION WAS.

Q. NOW, WOULD YOU TURN TO COLUMN -- COLUMN 17 AND 18 OF THAT PATENT. AND DO YOU SEE THAT TOWARD THE BOTTOM OF COLUMN 17 GOING ON OVER INTO THE TOP OF COLUMN 18 THERE IS A DISCUSSION OF THE VARIOUS THINGS THAT THE PROBES, THE LABELED HYBRIDIZATION PROBES DESCRIBED IN THIS PATENT CAN BE USED FOR?

A. YES.

Q. AND BASICALLY IT SAYS THEY CAN BE USED TO DETECT "NUCLEOTIDE SEQUENCES OF BACTERIAL, VIRAL, FUNGAL, YEAST, MAMMAL, PARASITE ORIGIN IN CLINICAL SAMPLES."

GOES ONTO SAY IN THE NEXT PARAGRAPH, "CAN ALSO BE USED TO DETECT GENTIC DISEASES SUCH AS HLA-LINKED DISEASE, THALASSEMIAS, SICKLE CELL ANEMIA, ET CETERA."

IS THAT AN ACCURATE CHARACTERIZATION OF WHAT THESE PROBES WERE INTENDED FOR?

A. THAT'S WHAT IT SAYS THERE.

Q. WHEN IT SAYS NUCLEIC ACID SEQUENCES, THAT SIMPLY MEANS DETECT A SEQUENCE, AND I CAN JUST USE YOUR NOTEBOOK HERE, DETECT A SPECIFIC SEQUENCE WITHIN A PIECE OF DNA?

A. YES.

Q. AND IT WOULD -- IT WOULD DO THAT BY HYBRIDIZING WITH IT AS THAT IS SET FORTH IN STEPS D AND E OF THE '195?

A. YES, IT WOULD DO BY HYBRIDIZATION.

Q. OKAY. DR. MULLIS, LET ME SHOW YOU A COPY OF A DOCUMENT WE'VE MARKED AS EXHIBIT A-23.

A. YES.

Q. IS THAT AN ABSTRACT OF THE TALK THAT YOU PRESENTED AT THE COLD SPRING HARBOR MEETING IN THE SUMMER OF 1986?

A. I'M NOT SO CERTAIN THAT IT IS. IT DESCRIBES THAT -- I THINK IT DESCRIBES THAT TALK, BUT I REALLY -- I THINK YOU ASKED ME ABOUT THIS PASSAGE ONCE BEFORE. IT'S NOT LABELED AS NECESSARILY THAT PARTICULAR TALK AND I CAN'T -- YOU KNOW, I CAN'T REALLY BE SURE THIS ABSTRACT COULD HAVE DESCRIBED LOTS OF TALKS THAT I GAVE. IT VERY EASILY COULD BE THAT PARTICULAR TALK.

Q. AND THE OPENING LINE OF THAT ABSTRACT SAYS:

"WE HAVE DEVISED A SIMPLE METHOD WHERE BY NUCLEIC ACID SEQUENCE CAN BE AMPLIFIED IN VITRO APPARENTLY WITHOUT LIMIT."

A. THAT'S WHAT IT SAYS, MR. FIGG. COULD HAVE SAID WE HAVE DEVISED A CUMBERSOME, LENGTHY METHOD, BUT LESS PEOPLE WOULD HAVE BEEN INTERESTED.

Q. WHEN YOU SAID YOU HAD DEVISED A SIMPLE METHOD, YOU WEREN'T TELLING SOMETHING YOU DIDN'T THINK WAS TRUE, WERE YOU?

A. NO, IT IS A SIMPLE METHOD. IT'S VERY SIMPLE TO DO ONCE YOU KNOW HOW. I DID NOT SAY WE HAVE SIMPLY DEVISED A SIMPLE METHOD, HOWEVER, I SAID WE HAVE DEVISED A SIMPLE METHOD.

Q. LET ME SHOW YOU A COPY OF A DOCUMENT WE'VE MARKED AS EXHIBIT A-24. I THINK MR. PASAHOW ALSO ASKED YOU SOME QUESTIONS ABOUT THAT.

A. YES, I'M VERY FAMILIAR WITH THIS.

Q. THAT'S AN ARTICLE THAT YOU WROTE AND PUBLISHED IN THE SCIENTIFIC JOURNAL?

A. YES.

Q. AND WE'VE MADE A BLOW UP OF THE FIRST PAGE OF THAT DOCUMENT WHICH HAS BEEN MARKED AS A-162.

AGAIN, THIS -- THIS ARTICLE INDICATES THAT PCR IS AN ENZYMATIC REACTION THAT IS SIMPLE TO PERFORM; IS THAT CORRECT?

A. YES, IT DOES.

Q. AND IT ALSO SAYS ON THE FIRST PAGE THAT PCR THAT IT'S DIFFICULT TO FIND SITUATIONS IN WHICH IT WILL NOT WORK AND THAT FACT DERIVES FROM ITS COMBINATION OF THREE FAMILIAR PHENOMENA;

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IS THAT RIGHT?

A. YES, IT DOES.

Q. AND ONE OF THOSE PHENOMENA YOU DESCRIBE IN THE ARTICLE AS BEING THE ABILITY OF PRIMERS TO -- TO HYBRIDIZE TO COMPLEMENTRY REGIONS ON THE TEMPLATE STRANDS.

A. YES, IF I COULD GO BACK YOU SORT OF LEFT -- IT DOESN'T SAY SIMPLY COMBINATION OF THREE FAMILIAR PHENOMENA, IT SAYS FORTUITOUS COMBINATION. I THINK THAT REALLY HAS SOME BEARING ON WHERE YOU'RE HEADED. I THINK IT MIGHT BE WELL TO READ IT COMPLETELY.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) DOCTOR, DO YOU AGREE THAT EVEN TODAY THERE ARE NO STANDARD CONDITIONS FOR CARRING OUT PCR THAT OFTEN SCIENTISTS HAVE TO EXPERIMENT IN OPTIMIZE CONDITIONS TO FIND A SET OF CONDITIONS THAT GIVES SATISFACTORY RESULTS?

A. I WOULD SAY THAT THERE'S CERTAINLY MORE STANDARD CONDITIONS AVAILABLE TODAY THAN PRIOR TO 1984, BUT A LOT OF SCIENTISTS PREFER TO EXPERIMENT OCCASIONALLY WHEN THEY DO A REACTION AND GET A RESULT THEY DON'T BELIEVE IS THE BEST POSSIBLE RESULT THEY COULD GET AND I'M CERTAIN THAT SOMETIMES THEIR EXPERIMENTATION ENDS UP IN MODIFYING GOOD REACTION IN A WAY THAT PERHAPS IMPROVES THEIR PARTICULAR EXPERIMENT.

THERE ARE -- THERE ARE CONDITIONS, HOWEVER, WHICH ARE NOW LAID OUT FULLY IN THIS PATENT AND IN OTHER LITERATURE WHICH IF YOU FOLLOW THOSE PARTICULAR RECIPES YOU WILL GET A RESULT IN

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JUST ABOUT ANY PLACE. THAT'S WHAT I HADN'T FOUND ANY PLACE WHERE I CAN'T GET AN AMPLIFICATION PRODUCT TO OCCUR. NO SEQUENCE THAT I'VE EVER TRIED TO AMPLIFY HAS BEEN RESILIENT TO THE PROTOCOLS THAT I'VE DEVELOPED WITH PCR.

Q. THIS IS THE REASON YOU CONSULT WITH A NUMBER OF COMPANIES AND INSTITUTION ON PCR SO THAT YOU CAN SHARE YOUR EXPERIENCES WITH THEM AND HELP THEM GET THEIR PCR REACTIONS TO WORK?

A. I USUALLY CONSULT WITH THEM AROUND SOME USE OF PCR RECOMMENDING WAYS THAT THEY CAN USE IT AND ACTUALLY CONDITIONS THAT THEY CAN EMPLOY THAT WILL IMPROVE THEIR PARTICULAR SITUATION, YEAH.

Q. DOCTOR, WOULD YOU TURN TO PAGE 242 OF THE EXHIBIT THERE THAT YOU HAVE BEFORE YOU. I THINK IT'S -- EXCUSE ME -- EXHIBIT A-24.

A. OKAY.

Q. YOU SEE THAT YOU DESCRIBED IN THE SECTION PRECEDING THIS THE END OF THE SECOND TO THE LAST PARAGRAPH HERE A NUMBER OF DIFFERENT CONDITIONS THAT SCIENTISTS MIGHT WORK WITH TO OPTIMIZE OR USE THE PCR TECHNIQUE?

A. YES, I WAS DESCRIBING A LOT OF -- I THINK IT'S IN THIS PARAGRAPH . . . YES, THAT'S TRUE, I WAS DESCRIBING THE FACT THAT A LOT -- THERE WERE A LOT OF PROTOCOLS AROUND.

Q. BUT YOU CONCLUDED BY SAYING NONE OF THESE PARAMETERS HAVE BEEN STUDIED SUFFICIENTLY BY ANYBODY TO RAISE THE LEVEL OF THIS DISCUSSION EARLIER THAN JUST THE LOCAL GOSSIP ON THE PCR CIRCUIT AND THE REASON FOR THIS IS PERHAPS THAT MOST OF THE TIME NO SUCH

EFFORTS ARE NECESSARY. THAT THE FRAGMENTS MELT EASILY BELOW 95 DEGREES AND THE REACTION WORKED FINE UNDER ANY REASONABLE CONDITIONS.

A. YES. REASONABLE THEY'RE CERTAINLY THE PEOPLE READING THIS PAPER UNDERSTOOD REASONABLE TO INCLUDE THOSE CONDITIONS THAT WOULD GET PCR TO WORK. NOT SOMETHING YOU KNOW COMPLETELY STRANGE.

Q. YEAH. IF IT WASN'T COMPLETELY STRANGE IN MOST CASES IT WORKS?

A. IF IT WAS NOT COMPLETELY STRANGE FROM THE POINT OF VIEW OF SOMEONE WHO KNOWS THE PROCEDURES THAT MAKE PCR WORK. COMPLETELY STRANGE HAS TO BE TAKEN IN THE CONTEXT OF, YOU KNOW, POST PCR TECHNOLOGY DAYS.

WHAT SEEMS COMPLETELY STRANGE TO SOMEONE WHO'S DOING PCR IN THE 1990'S WHEN THIS WAS WRITTEN WOULD NOT HAVE NECESSARILY SEEMED STRANGE TO SOMEONE IN 1969 OR TO SOMEONE IN 1983.

Q. AND YOU CHOSE TO DESCRIBE THAT AS SAYING THE REACTION WORKED FINE UNDER ANY REASONABLE CONDITIONS, THAT WAS YOUR LANGUAGE?

A. YES, I THINK PEOPLE WERE READING THIS UNDERSTOOD EXACTLY WHAT I MEANT BY THAT.

MR. FIGG: WE HAVE NO FURTHER QUESTIONS. THANK YOU, DR. MULLIS.

THE COURT: MR. PASAHOW, ANY REDIRECT?

MR. PASAHOW: YES, YOUR HONOR.

THE COURT: ABOUT HOW LONG?

MR. PASAHOW: I WOULD ESTIMATE I HAVE ABOUT A HALF AN HOUR.

THE COURT: I THINK THEN WHAT WE'LL DO IS WE'LL TAKE A RECESS NOW RATHER THAN GET STARTED ON THAT AND THEN PROCEED WITH THE REDIRECT AND THE RECROSS.

YOU MAY STEP DOWN. THANK YOU.

LADIES AND GENTLEMEN, PLEASE FOLLOW THE INSTRUCTIONS. WE'LL TAKE OUR RECESS AT THIS TIME FOR ABOUT TEN, 15 MINUTES.

(RECESS TAKEN)

(CONTINUED ON NEXT PAGE, NOTHING OMITTED)

(OPEN COURT, JURY PRESENT, AT 9:51 A.M.:)

MR. FIGG: ONE HOUSEKEEPING MATTER, YOUR HONOR:

I BELIEVE WHEN EXHIBIT 186, THIS -- THIS DOCUMENT, THIS POSTER HERE, WAS MARKED, IT WAS MARKED AS B-186. IT SHOULD HAVE BEEN MARKED AS A-186.

THE COURT: YOU'RE NOT MOVING THAT IN EVIDENCE, THOUGH.

MR. FIGG: WE WILL, YES, BUT --

THE COURT: OH, YOU WILL.

MR. FIGG: YEAH. I WAS JUST SAVING THAT FOR THE END.

THE COURT: I SEE.

MR. PASAHOW: AS LONG AS IT'S --

MR. FIGG: WE CAN DO IT NOW, IF YOU LIKE.

THE COURT: WHY DON'T WE CONSIDER IT DONE.

ANY OBJECTION?

MR. PASAHOW: NO, YOUR HONOR.

THE COURT: IT'S ADMITTED.

(PLAINTIFF'S EXHIBIT A-186
RECEIVED IN EVIDENCE)

MR. FIGG: WE HAVE --

THE COURT: WE'LL TAKE CARE OF IT LATER.

MR. FIGG: LATER. OKAY.

THE COURT: WE HAVE THAT ONE OUT OF THE WAY. OKAY.

(PAUSE IN PROCEEDINGS)

(CONTINUED ON NEXT PAGE, NOTHING OMITTED)

REDIRECT EXAMINATION

BY MR. PASAHOW:

Q. DR. MULLIS, YOU SPENT SOME TIME THIS MORNING TALKING ABOUT WHAT YOU UNDERSTAND CLAIM 1 TO COVER.

CLAIM 1 STARTS OUT DESCRIBING YOUR INVENTION AS:

"A PROCESS FOR AMPLIFYING AT LEAST ONE SPECIFIC NUCLEIC ACID SEQUENCE."

WHAT DID YOU MEAN BY "AMPLIFY"?

A. WELL, I ACTUALLY -- I THINK I DEFINED THE WORD PRETTY WELL AT THE VERY BEGINNING OF THE '202 PATENT, IN THE VERY FIRST PARAGRAPH, SO AS TO MAKE IT REALLY CLEAR WHAT I WAS TALKING ABOUT.

I JUST -- LET ME JUST READ THAT. IT'S VERY SHORT.

"THE PRESENT INVENTION RELATES TO A PROCESS FOR AMPLIFYING EXISTING NUCLEIC ACID SEQUENCES. MORE SPECIFICALLY, IT RELATES TO A PROCESS FOR PRODUCING ANY PARTICULAR NUCLEIC ACID SEQUENCE FROM A GIVEN SEQUENCE OF DNA OR RNA IN AMOUNTS WHICH ARE LARGE COMPARED TO THE AMOUNT INITIALLY PRESENT."

SO I THINK THAT -- THAT PARAGRAPH VERY CLEARLY DEFINES "AMPLIFY" AS MEANING TO MAKE A LARGE AMOUNT OF SOMETHING OUT OF A SMALL AMOUNT OF IT THAT'S INITIALLY PRESENT.

IS THAT -- THAT'S IN THE PATENT. THAT'S HOW YOU INTERPRET THAT, THE USE OF AMPLIFYING THERE IN THE CLAIM.

Q. SO HOW DOES YOUR -- YOUR INVENTION MAKE . . . WHAT WAS THE

LANGUAGE THAT YOU READ US?

A. IT SAYS --

Q. OH, I SEE.

A. -- IT PRODUCES A LARGE -- LET'S SEE.

"MORE SPECIFICALLY, IT RELATES TO A PROCESS FOR PRODUCING ANY PARTICULAR NUCLEIC ACID SEQUENCE FROM A GIVEN SEQUENCE OF DNA OR RNA IN AMOUNTS WHICH ARE LARGE COMPARED TO THE AMOUNT INITIALLY PRESENT. "

Q. AND WHAT'S THE AMOUNT ORIGINALLY PRESENT? THAT'S IN THE TARGET SEQUENCE?

A. THAT WOULD BE THE TARGET SEQUENCE.

Q. NOW, WHEN YOU WERE TESTIFYING YESTERDAY, YOU TOLD MR. FIGG THAT YOU WOULD BELIEVE THAT A PROCESS WOULD BE PCR IF IT WERE ABLE TO SHOW THAT THERE WAS SYNTHESIS USING A RELIABLE DETECTION SYSTEM.

WHAT DO YOU CONSIDER TO BE A RELIABLE DETECTION SYSTEM FOR A PCR AMPLIFICATION PROCESS?

A. WELL, THAT -- I PROBABLY -- I COULD GIVE YOU SOME EXAMPLES.

"RELIABLE" WILL HAVE A -- I MEAN, "RELIABLE" CAN HAVE ALL KINDS OF DEPTH OF MEANING, BUT I CAN SHOW YOU -- A RELIABLE METHOD WOULD HAVE TO BE ONE THAT -- IN THIS CASE, THAT INDICATED THAT THE -- THAT THE CLAIM -- THAT THE ELEMENTS OF THE CLAIM WERE -- WERE ALL BEING INCLUDED.

LET -- CAN I -- IS THERE A POSSIBILITY --

Q. SURE.

A. -- OF SHOWING . . .

(PAUSE IN PROCEEDINGS)

THE WITNESS: WE WERE TALKING ABOUT -- I THINK MR. FIGG WAS -- IT WAS WHEN I WAS TALKING WITH HIM ABOUT THE METHOD WHICH I EMPLOYED TO DETERMINE THAT AN AMPLIFICATION HAD TAKEN PLACE IN THE CASE OF EXAMPLE 1 IN THE -- IN THE '202.

AND THE METHOD THAT I USED WAS TO LOOK FOR A 25-BAND -- 25-BASE PAIR BAND ON A GEL.

I DON'T SEEM TO HAVE ANYTHING TO DRAW WITH.

(PAUSE IN PROCEEDINGS)

THE WITNESS: AND THAT -- THE FACT THAT PRESENCE OF THAT 25-BASE PAIR BAND ON THE GEL WOULD BE RELIABLE, WOULD BE A RELIABLE INDICATION THAT THE CLAIMS WERE BEING FULFILLED, MEANING THAT THE PRODUCTS OF THE PRIMER EXTENSION IN ONE CYCLE WERE BEING USED AS TEMPLATES IN THE OTHER CYCLE.

THE REASON THAT WOULD BE A RELIABLE METHOD TO SHOW THAT IS BECAUSE THAT PROCESS, AS I WAS USING IT IN THAT EXPERIMENT, WAS PRODUCING A 25-BASE PAIR BAND THAT DIDN'T PREVIOUSLY EXIST.

IT WASN'T STARTING WITH A 25-BASE PAIR PIECE OF DNA AND TRYING TO MAKE A LITTLE BIT -- TEENY LITTLE BIT MORE OF IT. IT WAS STARTING WITH A MIXTURE THAT HAD NONE OF THAT 25-BASE PAIR BAND IN THAT AND IT WAS TRYING TO CREATE THAT.

SO THE EXISTENCE OF THAT THING ON THE GEL TOLD ME FAIRLY RELIABLY THAT, IN FACT, THE PROCESS HAD WORKED.

AND IT'S A MATTER OF -- THE FIRST CYCLES IN THAT

REACTION . . . THE FIRST CYCLE IN THAT REACTION PRODUCED THIS (INDICATING) AND THAT (INDICATING); RIGHT? I GOT THIS (INDICATING) . . . AND THEN I GOT THAT (INDICATING).

AND THE SECOND CYCLES . . . I PRODUCED THIS (INDICATING) AND THAT (INDICATING).

THE THIRD CYCLE, FROM THESE (INDICATING), BEING PRIMED BY THE PROCESS THAT'S HERE -- BEING PRIMED BY -- IT'S -- ACTUALLY, I DREW THAT WRONG.

THIS WOULD BE THE PRIMER (INDICATING); IT WOULD PRODUCE THAT (INDICATING).

AND THEN ACTING ON THESE (INDICATING), I BEGIN TO GET THE ACCUMULATION IN THE THIRD CYCLE, 25-BASE PAIR PIECES OF DNA.

THIS IS KIND OF HARD TO DRAW ON.

BUT NOW THESE THINGS HAD NOT EXISTED TO START WITH, AND THEY COULD ONLY BE MADE BY A TWO -- TWO EXTENSION PROCESSES, ONE WHERE THE PRIMER WAS EXTENDED ON THE LONG STRAND MAKING THE LONG PRODUCT, AND THEN ANOTHER WHERE THE LONG PRODUCT WAS PRIMED AND EXTENDED AGAIN.

THAT'S THE FIRST TIME I SAW THE 25-BASE LONG PIECE OF DNA.

AND THEN THE THIRD CYCLE, THAT BEING PRIMED AND EXTENDED WOULD GIVE ME A 25-BASE PAIR FRAGMENT.

SO WHEN I SAW THE 25-BASE PAIR FRAGMENT ON THE GEL, THAT WAS A GOOD INDICATION, A FAIRLY RELIABLE INDICATION. I WOULDN'T WANT THAT -- I WOULD NOT HAVE RISKED MY LIFE ON THAT

BEING TRUE. IT'S NOT THAT RELIABLE. IT'S ABOUT AS RELIABLE AS, SAY, A TOASTER OR SOMETHING. YOU DON'T HAVE TO HAVE AN ABSOLUTELY RELIABLE TOASTER.

I WAS READY TO SAY THE PROCESS WORKED AT THAT POINT. I THOUGHT THAT WAS A RELIABLE DETECTION SYSTEM.

I WENT FURTHER AND DESIGNED OTHER EXPERIMENTS THAT WOULD TRY TO SAY: IS THIS 25-BASE PAIR PIECE REALLY WHAT I THINK IT IS?

AND I -- I WORKED ON THAT AND REALIZED THAT THIS WAS TOO SHORT A PIECE TO DO A LOT OF SORT OF PICKING APART, SO I STARTED MAKING BIGGER PIECES THAT I COULD REALLY CUT IN SEVERAL PLACES AND LOOK AT THE FRAGMENTS AND SAY: DID THAT LOOK LIKE THE ONES I WANTED THAT I HAVE?

AND BY THE TIME I GOT AROUND TO PUBLISHING FOR MY COLLEAGUES TO EXAMINE IN THEIR VERY SORT OF, YOU KNOW, PICKY WAY MY WORK, I HAD LOTS OF DATA THERE THAT SHOWED THEM EXACTLY RELIABLY THAT THE PROCESS HAD, IN FACT, WORKED AS ADVERTISED. OTHERWISE, THE PAPER WOULD PROBABLY NOT HAVE BEEN PUBLISHED, OR I WOULDN'T HAVE TRIED TO PUBLISH IT IF I DIDN'T HAVE THAT KIND OF INFORMATION.

SO THAT -- "RELIABLE" MEANS A LOT OF DIFFERENT KIND OF THINGS, BUT CLEARLY IT -- THINGS THAT THE TEST THAT YOU'RE USING TO FIND OUT WHAT'S HAPPENING IS REALLY GOING TO TELL YOU WHAT'S HAPPENING.

IF IT WAS -- IF I WAS USING A TEST THAT WAS JUST --

WHERE ANYTHING THAT HAD HAPPENED WOULD SHOW UP AS A POSITIVE RESULT, I DON'T THINK THAT -- THAT WOULDN'T HAVE BEEN RELIABLE, AND I COULD HAVE BEEN FOOLED INTO THINKING I WAS DOING SOMETHING THAT I REALLY WASN'T DOING. SO . . .

Q. (BY MR. PASAHOW) BEFORE YOU LEAVE THAT:

ON THE 25-BASE PAIR PIECE, DOES THAT SHOW YOU THAT YOU'RE USING THE PRODUCT OF ONE CYCLE AS TEMPLATE IN THE LATER CYCLE?

A. YES. YES, IT DOES, MR. PASAHOW. I THINK THAT IT SHOWS THAT -- IT -- THE ONLY WAY THAT I CAN IMAGINE YOU'D GET A 25-BASE PAIR PIECE THERE -- I MEAN, THERE MIGHT BE SOME OTHER WAY. THAT'S WHY I HAD TO GO LOOK AT IT AND MAKE SURE IT WAS THE RIGHT ONE.

BUT THAT ABOUT -- THAT'S THE ONLY WAY YOU CAN GET A 25-BASE PAIR FRAGMENT STARTING AT -- THIS PLASMID IS 5,000 BASE PAIRS. THESE LONG PRODUCTS WERE WHO KNOWS HOW MANY BASE PAIRS, SOME OF THEM PROBABLY HUNDREDS.

ONLY AFTER THREE CYCLES WHERE THEY -- THE EXTENSION PRODUCT WAS OF -- OF ONE PRIMER WAS BEING PRIMED BY THE OTHER PRIMER AND THAT WAS GETTING EXTENDED, ONLY THEN WOULD I START GETTING 25 BASE PAIRS.

SO I COULD USE THIS AS A -- THE APPEARANCE OF THIS BAND IN ANY AMOUNT, REALLY, WAS -- WAS A RELIABLE INDICATOR THAT THE PROCESS WAS WORKING THROUGH TWO CYCLES AT LEAST, OR THREE, IN FACT, BEFORE I GOT A DOUBLE-STRANDED PIECE.

Q. ONE OTHER QUESTION:

YOU SAID AFTER YOU GOT THE LONGER PIECES, YOU SHOWED THAT THEY WERE WHAT YOU THOUGHT THEY WERE BY CUTTING THEM. WHAT DO YOU MEAN?

A. OH, OKAY. WELL, ONCE -- ONCE I GOT AWAY FROM THAT -- THE INITIAL SYSTEM, AND I STARTED MAKING THINGS THAT WERE, LIKE, 110 BASE PAIRS LONG, THEN THEY WOULD HAVE ENOUGH SEQUENCE INFORMATION IN THEM SUCH THAT I COULD FIND SEVERAL SITES THAT WERE -- THAT WERE A RESTRICTION ENZYME.

AND THEY HAVE CUTE LITTLE NAMES, BUT THIS -- I GOT -- IN THE PIECE THAT I WAS MAKING FROM THE BETA-GLOBIN REGION, THERE WERE THREE DIFFERENT RESTRICTION ENZYMES THAT I COULD EMPLOY. EACH OF WHICH WOULD -- WOULD MAKE ONE CUT IN THAT MOLECULE AT SOME SPECIFIC LOCATION,

AND I COULD SAY: OKAY. IF I TREAT THAT MOLECULE WITH MST II AND THEN I LOOK AT THE PRODUCTS OF THAT, I SHOULD SEE TWO MOLECULES ABOUT HALF AS BIG AS THE ORIGINAL ONE, AND THAT WOULD LOOK LIKE, ON A GEL, THE BIG ONE WOULD BE UP HERE (INDICATING) AND THEN THERE WOULD BE TWO LITTLE ONES DOWN THERE.

I'D SAY: OKAY. THAT'S PARTIAL DIGESTION. IF I CUT IT, I WOULD END UP WITH THESE TWO AND NO MORE OF THAT.

SO I SAY EVERYTHING I MADE THERE HAD AN MST II SITE IN THERE. THE MST II SITE LOOKS LIKE -- I'VE FORGOTTEN THE SEQUENCE. SOMETHING LIKE G-G, SAY, A-T-T-C.

THAT'S NOT MST II. IT'S SOMETHING LIKE THAT. IT'S A

SERIES OF SIX LETTERS THAT'S GOT TO BE THERE.

SO THE FACT THAT IT WOULD CUT WITH THAT INTO THESE TWO FRAGMENTS SAID THAT SITE IS SOMEWHERE OUT IN THE MIDDLE.

AND, IN FACT, WHEN I USED NCO2, IT WOULD CUT INTO TWO FRAGMENTS. ONE WOULD BE VERY LITTLE AND ONE WOULD BE VERY BIG.

AND I SAID: WELL, IT HAS GOT TO HAVE A SITE SOMEWHERE AT THE ENDS. AND THAT'S SORT OF WHAT I MEAN BY PICKING THE MOLECULE APART AND ANALYZING IT.

Q. WELL, THESE THINGS YOU'VE WRITTEN DOWN HERE, ARE -- THESE ARE DIFFERENT RESTRICTION ENZYMES?

A. YES.

Q. AND THEY CUT AT DIFFERENT SEQUENCES OF LETTERS?

A. YES. DIFFERENT SEQUENCE -- I CAN'T REMEMBER WHAT THEY ARE, ACTUALLY. IT'S BEEN AWHILE.

Q. BUT THE FACT THAT IT WOULD CUT WOULD PROVE TO YOU THAT THAT SEQUENCE OF LETTERS WAS THERE SOMEWHERE.

A. YES, IT WAS. IT WAS -- IT WAS A WAY OF GETTING PARTIAL SEQUENCE INFORMATION ABOUT THE MOLECULE THAT I HAD MADE.

(WITNESS RESUMES WITNESS STAND.)

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, MR. FIGG SHOWED YOU A POSTER THAT HAD SOME PRIMERS FROM YOUR EXAMPLES. IT WAS EXHIBIT A-185.

A. YES.

Q. AND THAT HAS DOWN AT THE BOTTOM A -- IT SHOWS THAT THERE ARE TWO BASES AT THE END OF THE PRIMERS YOU USED FOR EXAMPLE 4 WHICH

OVERLAPPED.

A. (NODDING HEAD.)

Q. AND TAKING THAT AS A SAMPLE OF HOW THIS WORKS, HOW LONG WAS THE PIECE YOU WERE LOOKING FOR IN EXAMPLE 4?

A. IN EXAMPLE 4, I THINK WE WERE MAKING A 240-BASE PAIR PIECE. LET ME CHECK THAT.

(PAUSE IN PROCEEDINGS)

THE WITNESS: YEAH, IT SAYS:

"THIS EXAMPLE ILLUSTRATES AMPLIFICATION OF A 240-BASE PAIR SEQUENCE SPANNING THE ALLELIC MST II SITE . . ."

AND THAT SAME BETA-GLOBIN GENE, IT WAS 240 BASES LONG. I'M GETTING BETTER AT IT AND I'M MAKING BIGGER PIECES NOW.

Q. (BY MR. PASAHOW) NOW, WAS THAT 240-BASE PAIR PIECE IN THE SOLUTION WHEN YOU STARTED THE AMPLIFICATION?

A. NO, IT WOULDN'T HAVE BEEN IN THE SOLUTION. IT WAS LIKE -- THIS AMPLIFICATION, I WAS STARTING WITH A -- AGAIN, A . . . WITH -- I THINK THIS -- IN THIS PARTICULAR ONE, I HAD IT IN A PLASMID. I MAY HAVE HAD IT IN -- IN HUMAN DNA, BUT IT CERTAINLY DID NOT HAVE A 240-BASE PAIR FRAGMENT IN IT.

Q. SO WHAT YOU WERE LOOKING FOR AT THE END WAS WHETHER THERE WAS A 240-BASE PAIR LONG PIECE ON A GEL?

A. YES, AND THAT 240-BASE PAIR PIECE WOULD HAVE HAD TO CUT INTO SPECIFIC FRAGMENTS, THE SAME WAY AS THE OTHER ONE, FOR ME TO REALLY BELIEVE FOR SURE THAT IT WAS WHAT IT WAS. FOR MY

COLLEAGUES. I REALLY BELIEVED IT.

Q. NOW, IF THIS HAD FORMED AND THESE TWO ENDS HAD EXTENDED, WOULD YOU HAVE BEEN ABLE TO TELL THE DIFFERENCE BETWEEN THAT AND THE 240-BASE PAIR PIECE YOU WERE LOOKING FOR?

A. YES. THAT WOULD HAVE MADE ABOUT A 40, I THINK, BASE PAIR FRAGMENT, WHICH WOULD HAVE APPEARED VERY MUCH NEAR THE BOTTOM OF THE GEL, WHEREAS THE 240-BASE PAIR FRAGMENT THAT I WAS TRYING TO MAKE WOULD HAVE APPEARED MUCH CLOSER TO THE TOP OF THE GEL THAT I WAS USING.

OF COURSE, THE 40-BASE PAIR PIECE WOULD NOT HAVE CUT INTO THE APPROPRIATE PIECES, EITHER. IT WOULD HAVE BEEN VERY EASY TO DISTINGUISH THOSE TWO THINGS.

Q. NOW, MR. FIGG ALSO SHOWED YOU THIS PAGE FROM YOUR NOTEBOOK, EXHIBIT . . . A-186.

AND HE POINTED OUT THAT, IN ONE OF THE CORNERS, YOU'VE SHOWN THAT THE TWO PRIMERS YOU WERE USING COULD FORM THIS FUNNY LOOP STRUCTURE BUT THEY COULD ANNEAL TO EACH OTHER.

A. YES.

Q. AND YOU -- YOU INDICATED, I BELIEVE, THAT YOU ACTUALLY SAW ON A GEL A PIECE THAT YOU THOUGHT WAS THAT PIECE?

A. YES. I HAD BEEN SEEING IT QUITE A LONG TIME BEFORE I FIGURED OUT WHAT IT WAS. IT HAD BEEN KIND OF AN ANNOYING LITTLE THING.

IT ALWAYS -- ANY TIME I RAN A GEL THAT SUPPOSEDLY HAD HAD PURIFIED JB03, WHICH WAS THE NAME OF THAT PRIMER, I'D ALWAYS

GET A MAIN BAND THAT WAS RIGHT IN THE RIGHT PLACE, AND THEN I'D GET ANOTHER ONE, A LITTLE FAINT BAND UP ABOVE IT.

I COULD CUT THAT OUT OF THE GEL AND RE-RUN IT WITH THAT BAND. IT STILL GAVE ME THE OTHER ONE.

IT SHOULD HAVE INDICATED TO ME IT WAS SOME PROPERTY OF JB03 THAT HAD THOSE FORMS.

BUT, YES, IT WAS EASY TO PICK THAT OUT OF THE GEL AND SEE WHAT IT WAS.

Q. COULD YOU TELL THE DIFFERENCE BETWEEN WHAT YOU GOT WHEN THIS FORMED AND RAN ON THE GEL AND WHAT YOU GOT WHEN YOU GOT THE PRODUCT OF THE PCR REACTION?

A. YES. YEAH, THE PRODUCT OF THE PCR REACTION THAT I -- THAT I USED -- THAT I USED THAT FOR, I MEAN, THE ONE JB03 WAS IN -- WAS MAKING A 58-BASE PAIR PRODUCT, WHICH WAS EASY TO DISTINGUISH FROM THAT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, YOU ALSO REVIEWED WITH MR. FIGG EXHIBIT A-184, WHICH WAS A PORTION OF ONE PAGE OF YOUR NOTEBOOK. LET ME GET YOU THAT NOTEBOOK PAGE.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) SHOWING YOU THE -- ONE OF YOUR LABORATORY NOTEBOOKS, DOES THAT DRAWING APPEAR SOMEWHERE THERE?

A. YES. YES, IT DOES.

I MADE THAT DRAWING AS -- I USED -- I DID THESE ALL -- WHENEVER I WAS DOING EXPERIMENTS THAT WERE GOING TO HAVE ANY

KIND OF COMPLICATED -- I MEAN, WHERE THERE WERE STRUCTURES INVOLVED AND THINGS, I'D ALWAYS TRY TO MAKE MYSELF A NICE NEAT DIAGRAM OF WHAT THAT -- WHAT I WAS ABOUT TO DO SO -- JUST THAT I COULD USE IT TO -- I MEAN, AS A REFERENCE FOR ME.

Q. DID YOU --

A. THAT --

Q. GO AHEAD.

A. I WAS THROUGH.

Q. DID YOU EVER PUBLISH THIS DRAWING?

A. I DON'T THINK I EVER PUBLISHED THAT DRAWING AS . . . NO, I'M ALMOST SURE I NEVER PUBLISHED THAT DRAWING.

Q. DID YOU EVER USE THIS DRAWING TO TRY TO EXPLAIN THE PCR PROCESS TO SOMEONE?

A. NO. THIS -- I WOULD NOT HAVE USED THIS PARTICULAR DRAWING TO DESCRIBE THE PCR PROCESS TO ANYBODY, EVEN -- I WOULDN'T EVEN TRY TO USE THAT DRAWING TO DESCRIBE IT TO SOMEBODY TODAY WHO ALREADY UNDERSTOOD IT.

I -- YOU KNOW, I'VE GOT A PICTURE -- I HAD -- I MADE A PICTURE VERY SIMILAR TO THAT, EXCEPT THAT IT WAS MUCH MORE DETAILED. AND IT WAS A WAY -- I MEAN, I MADE IT ON THE COMPUTER THE SAME WAY, AND I -- IT WAS A PART OF THE '202, WHICH I THOUGHT WAS A VERY NICE DIAGRAM WHICH ANYBODY SEEING WOULD BE ABLE TO UNDERSTAND.

NOW, IT'S -- I THINK THIS IS SOMETHING THAT YOU'VE GOT IN YOUR BOOKS OVER THERE, BUT IT'S A LONG -- IT LOOKS KIND OF

FORMIDABLE AT FIRST, BUT IT REALLY --

Q. CAN YOU TELL US WHAT YOU'RE LOOKING AT?

A. OH. IT'S FIGURE -- IT'S CALLED SHEET 4 OF 12. IT'S ABOUT -- IT'S IN THE '202 PATENT, AND IT'S ABOUT THREE OR FOUR PAGES FROM THE BEGINNING.

IT'S ONE OF THE -- ONE OF THESE -- IT'S THIS THING (INDICATING) THAT'S GOT A LOT OF LETTERS IN A LINE AND THEN IT'S ABOUT THREE PAGES OF THAT STUFF.

AND AT FIRST GLANCE, IT MIGHT LOOK, YOU KNOW, COMPLICATED, BUT IT REALLY IS NO MORE COMPLICATED THAN IT NEEDS TO BE TO DESCRIBE THE ELEMENTS OF THE CLAIM THAT'S DESCRIBED IN THE '202.

AND IT -- IT SHOWS THE ORIGINAL DUPLEX -- IT SHOWS THE ORIGINAL DUPLEX, STRANDS OF IT BEING SEPARATED AND THEN PRIMED. IT SHOWS WHAT THE EXTENSION PRODUCTS LOOK LIKE.

AND THE LITTLE NUMBERS OVER IN THE LEFT COLUMN REFER TO WHICH CYCLE IT WAS THAT THAT PARTICULAR PRODUCT APPEARED. SO YOU CAN GO DOWN FROM THE ORIGINAL DUPLEX HAS ZERO ZERO BESIDE IT, AND THEN YOU SEE THE ELEMENTS OF THE DUPLEX, THE TWO STRANDS BEING PRIMED, STILL ZERO ZERO, AND THEN THE ONE ONE ARE THE LONG PRODUCTS FROM THAT FIRST EXTENSION.

Q. COULD -- I THINK IT WOULD HELP IF YOU CAME DOWN AND POINTED OUT THESE PORTIONS YOU'RE SHOWING.

A. YOU WANT ME TO COME DOWN?

(PAUSE IN PROCEEDINGS)

THE WITNESS: LET ME GET THE STICK HERE.

OKAY. SO IT'S THE SAME KIND OF DIAGRAM. I MADE IT IN THE SAME WAY, SITTING THERE ON A WORD PROCESSOR, BASICALLY, DRAWING ALL THESE -- MAKING ALL THESE LITTLE LETTERS.

AND IT DEMONSTRATES -- SEE, THESE LITTLE NUMBERS OVER HERE ARE -- THIS IS THE CYCLE NUMBER IN WHICH THAT STRAND APPEARED -- OKAY? -- SO WE CAN TAKE THE DUPLEX, WE WOULD DENATURE IT, WE'D PRIME IT WITH THESE TWO GUYS, AND WE EXTEND THEM, AND THEN WE MELT IT AGAIN.

THAT'S WHAT THESE -- THESE ARE THE PRODUCTS OF CYCLE 1.

THEN WE SEE IN CYCLE 2 THAT YOU MELT AGAIN, YOU GET FOUR SINGLE STRANDS, TWO OF WHICH ARE THE ORIGINAL DUPLEX, AND THE OTHER TWO OF WHICH HAVE JUST BEEN SYNTHESIZED, THIS ONE (INDICATING) AND THAT ONE (INDICATING).

NOW YOU SEE THE PRIMER -- THIS PRIMER PRIMING ON A STRAND WHICH IS THE EXTENSION PRODUCT OF THE OTHER PRIMER FROM THE LAST CYCLE.

OKAY. AND AS YOU -- YOU CAN SEE FROM THIS DIAGRAM THAT, WHEN IT GETS EXTENDED ON THAT, IT'S GOING TO MAKE A PIECE OF DNA THAT HAS A SPECIFIC LENGTH.

OKAY. SO THAT WAS REAL IMPORTANT TO ME TO DEMONSTRATE THAT THAT, IN FACT, HAPPENED.

AND ON THE NEXT PAGE, IF WE CAN SEE THAT. IT TOOK THREE PAGES TO REALLY DESCRIBE THIS WHOLE CYCLE TO PEOPLE. AND I CAN'T REMEMBER EXACTLY WHAT MONTH I FIRST MADE THIS DIAGRAM.

I DID VARIOUS ONES LIKE IT.

BUT YOU CAN SEE THE WHOLE PROCESS GOING IN. CYCLE 1, YOU END UP WITH THESE PIECES (INDICATING). THESE ARE THE PRODUCT, THESE RIGHT HERE (INDICATING), WHICH ARE PRIMED AND END UP BEING PRODUCT OF -- IN CYCLE -- AFTER YOU'VE DONE THE SECOND EXTENSION. YOU GET THESE. SEE, THESE HAVE LITTLE TWOS BESIDE THEM.

YOU GET TWO MORE LONG PRODUCTS, AND YOU GET TWO SHORT PRODUCTS ON THE LINE.

AND THEN AFTER THE THIRD CYCLE, WHICH YOU GET -- WE CAN GO THROUGH THAT RATHER QUICKLY. BUT ON THE VERY NEXT PAGE, YOU CAN SEE THE PRODUCTS OF CYCLE 3 ARE FINALLY THESE CUTE LITTLE DUPLEX DNA MOLECULES WHICH HAVE SPECIFIC LENGTHS, SEE? AND ONE OF THE STRANDS FROM THAT WAS ADDED IN 3; THE OTHER ONE IN 2.

THIS -- THIS IS A DIAGRAM THAT I WOULD USE.

AND THEN BELOW THIS -- IF YOU'D SLIDE IT UP JUST A LITTLE FURTHER -- I HAVE A CHART THAT SHOWS WHAT HAPPENS, HOW MANY COPIES YOU END UP WITH OF THE VARIOUS THINGS, AFTER ZERO, ONE, FIVE, 10, 15, 20 CYCLES.

SO I TAKE -- I TOOK -- THIS IS THE KIND OF DIAGRAM THAT I WOULD USE TO DESCRIBE PCR, AND I -- AND I FEEL IT'S PRETTY EXPLICIT.

BUT I TOOK THIS DIAGRAM, OR ONES LIKE IT, AROUND FOR SIX MONTHS IN 1983, AFTER I KNEW THIS PROCESS WOULD WORK AND I UNDERSTOOD WHAT IT WOULD DO, AND I COULDN'T GET ONE SINGLE

SCIENTIST -- OKAY? -- TO LOOK AT THIS, AND EVEN WITH ALL THAT EXPLICIT DETAIL, SAY, "YEAH, YOU'RE ONTO SOMETHING, MULLIS."

AND THOSE PEOPLE WERE NOT --

MR. FIGG: YOUR HONOR, DR. MULLIS IS GOING QUITE FAR BEYOND THE QUESTION.

THE WITNESS: OKAY.

THE COURT: YES.

THE WITNESS: I THOUGHT I WAS ANSWERING THE QUESTION OF WHETHER I WOULD USE A DIAGRAM LIKE THAT TO DESCRIBE PCR.

THE COURT: OKAY.

THE WITNESS: IT'S HARD TO DESCRIBE PCR.

THE COURT: WHY DON'T -- OKAY. WE'LL WAIT FOR ANOTHER QUESTION NOW. THANK YOU.

Q. (BY MR. PASAHOW) WELL, WHY DON'T I ASK: WHAT WAS THE REACTION WHEN YOU USED THIS ELABORATE DIAGRAM TO TRY AND EXPLAIN THE PCR PROCESS TO YOUR PEERS AT CETUS?

A. WELL, EVEN WITH THAT ELABORATE DIAGRAM, WHAT I WAS SAYING WAS THAT MY COLLEAGUES AT CETUS DID NOT RESPOND -- THEY STILL COULDN'T SEE THE PCR PROCESS. IT'S A COMPLICATED THING.

SHOULD I GO BACK IN THE BOX?

Q. YES.

(LAUGHTER)

THE WITNESS: (WITNESS RESUMES WITNESS STAND.)

AND THOSE PEOPLE WERE NOT SCIENTISTS OF ORDINARY SKILL, AS ATTESTED TO BY THE FACT THAT MORE THAN ONE OF THEM HAVE NOW

EDITED BOOKS DESCRIBING USES OF THE POLYMERASE CHAIN REACTION. IT TOOK THEM A LONG TIME TO CATCH ON, WITH AN EVEN MORE COMPLICATED DIAGRAM THAN -- I MEAN, A MORE EXPLICIT DIAGRAM THAN THAT.

DOES THAT ANSWER THE QUESTION?

Q. (BY MR. PASAHOW) YES.

A. OKAY.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) MR. FIGG ALSO SHOWED YOU ONE OF THE PAGES FROM YOUR NOTEBOOK INVOLVING THE VERY FIRST EXPERIMENT YOU DID.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) AND HE POINTED OUT THAT, IN THE COURSE OF THIS EXPERIMENT, YOU DESCRIBED SEVERAL BUFFER FORMULAS, ONE OF WHICH YOU GOT APPARENTLY FROM TEXTS BY FINEBERG AND VOGELSTEIN, AND ONE OF WHICH YOU GOT FROM BIOLABS FOR KLENOW.

NOW, ARE THESE THE FORMULAS THAT YOU USED, THESE FORMULAS YOU WROTE DOWN HERE ON THIS PAGE?

(PAUSE IN PROCEEDINGS)

THE WITNESS: THEY'RE -- I USED A -- I'VE USED PROBABLY A LOT OF DIFFERENT BUFFER FORMULAS. I MEAN, I HAD EMPLOYED MANY DIFFERENT BUFFERS BY, YOU KNOW, AFTER -- I MEAN, BY NOW. I'M NOT SURE WHEN I USED THEM.

BUT I -- THOSE ARE BUFFER FORMULAS THAT I JUST COLLECTED, SORT OF LIKE YOU COLLECT A BUNCH OF RECIPES. IT GAVE ME SOME IDEAS ABOUT, YOU KNOW, BUFFERS.

AND I AT THAT POINT WAS NOT ALL THAT -- I WAS NOT REALLY THAT CONCERNED ABOUT THE BUFFER, BUT I DID REALIZE THAT I MIGHT OUGHT TO HAVE A FEW POSSIBILITIES IF SOMETHING DIDN'T WORK, AND I FINALLY GOT AROUND TO THINKING, MAYBE IT'S THE BUFFER. THEN I MAYBE TRIED ANOTHER BUFFER, BUT . . .

I -- I DIDN'T -- I DON'T REMEMBER USING ANY ONE OF THOSE, BUT THERE WAS LOTS OF THEM IN THERE I COULD HAVE USED.

Q. MR. FIGG ALSO SHOWED YOU ANOTHER PAGE OF YOUR NOTEBOOK WHERE YOU WERE DOING THAT SECOND UNSUCCESSFUL EFFORT AT PCR.

AND THERE -- THIS WAS THE FIRST CYCLING REACTION.

AND THERE, YOU SAY . . . I THOUGHT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) THAT IN THE COURSE OF THE CYCLING, YOU CHILLED THE SOLUTION ON ICE.

A. YES.

Q. DO YOU SEE THAT REFERENCE?

A. RIGHT.

Q. NOW, WAS THAT THE SAME PROCESS THAT WAS BEING USED IN THOSE ARTICLES THAT MR. FIGG WENT THROUGH WITH DR. SMITH?

A. NO. THE -- IN THOSE ARTICLES, THE PURPOSE OF CHILLING IT ON -- CHILLING ON ICE WAS TO PREVENT THE REASSOCIATION OF THE -- OF THE STRANDS OF THE PLASMID, THE DOUBLE-STRANDED PLASMID THAT THEY WERE SEQUENCING WITH.

IN THIS REACTION, I WAS STARTING WITH WHOLE HUMAN DNA, WHICH I COULD HAVE HEATED IT AND COOLED IT DOWN TO ROOM

TEMPERATURE AND LEFT IT FOR A WEEK AND THE STRANDS STILL WOULD NOT HAVE FOUND EACH OTHER, BECAUSE HUMAN DNA IS SO COMPLEX THAT UNTIL I HAD -- UNTIL ONE HAD AMPLIFIED PROBABLY A MILLION-FOLD, YOU WOULDN'T HAVE TO EVEN CONCERN YOURSELF WITH THE TEMPLATE STRANDS RE-ANNEALING. IT WAS -- THAT WAS NOT THE PURPOSE OF THAT.

I REALLY -- I THINK THE REASON I CHILLED IT RAPIDLY WAS, AT THAT POINT, I WAS NOT COMPLETELY SURE THAT THE -- THE NUCLEOTIDE TRIPHOSPHATES WERE STABLE AT A HIGH TEMPERATURE, AND I WANTED TO DROP THE TEMPERATURE AWAY FROM A HUNDRED AS FAST AS POSSIBLE TO PREVENT THEM FROM DEGRADING.

Q. NOW, THAT ONE -- THAT REACTION DIDN'T WORK, AND THEN WE DISCUSSED THE FIRST ONE THAT DID WORK WAS THE ONE THAT HAPPENED IN DECEMBER.

AND WHERE YOU DESCRIBE THE CYCLE HERE (INDICATING) AND THE HEATING AND COOLING, DID YOU COOL THAT ONE ON ICE?

A. NO, I -- I THINK I COOLED IT TO 32 DEGREES.

(PAUSE IN PROCEEDINGS)

THE WITNESS: I THINK THAT'S WHAT IT SAYS.

Q. (BY MR. PASAHOW) YOU SAY "COOL IN WATER BATH TO 32 DEGREES CENTIGRADE."

A. RIGHT. AND THERE, YOU NOTICE I STARTED AT 85. SO THE DEOXYNUCLEOTIDE -- THE NUCLEOTIDE TRIPHOSPHATES HAD NOT BEEN HEATED TO A HUNDRED. I WASN'T QUITE -- I WASN'T AS WORRIED ABOUT THE STABILITY AT 85 AS I WAS AT A HUNDRED.

Q. AND FOR -- IN CASE OTHERS HAVE THE SAME PROBLEM I DO, IS 32 DEGREES CENTIGRADE FREEZING?

A. IT'S WARM. IT'S LIKE ALMOST -- IT'S A LITTLE BIT LESS THAN BODY TEMPERATURE.

Q. NOW, YOU INDICATED TO MR. FIGG THAT SOME OF THE EXAMPLES -- OR SEVERAL OF THE EXAMPLES INDICATE SPECIFICALLY THE ANNEALING TIME.

WOULD YOU LOOK AT EXAMPLE 2 AND SEE IF YOU CAN SHOW US WHERE THAT APPEARS.

A. IN THE '202 . . .

Q. EXAMPLE 2 STARTS IN COLUMN 16.

A. OKAY. WELL . . .

(PAUSE IN PROCEEDINGS)

THE WITNESS: OKAY. THAT ONE, WE GO INTO A LOT OF PRELIMINARIES THERE TELLING YOU ABOUT WHERE THE DNA COMES FROM, THE PRIMERS.

IT SAYS, "POLYMERASE CHAIN REACTION." IT SAYS . . . THAT WE HEATED --

> "EACH RESULTING SOLUTION WAS HEATED TO A HUNDRED DEGREES FOR FOUR MINUTES AND ALLOWED TO COOL TO ROOM TEMPERATURE FOR TWO MINUTES, WHEREUPON ONE MICROLITER CONTAINING FOUR UNITS OF KLENOW . . . POLYMERASE WAS ADDED."

SO THAT SAYS TWO MINUTES.

Q. (BY MR. PASAHOW) AND IN EXAMPLE 3, IS THERE ANY INDICATION

OF THE COOLING AND ANNEALING TIME?

A. THERE, IT SAYS FOR ONE MINUTE. IT SAYS THE SOLUTION WAS HEATED -- NO.

IT SAYS: ". . . TO A HUNDRED DEGREES CENTIGRADE FOR ONE MINUTE AND BROUGHT RAPIDLY TO 25 DEGREES C FOR ONE MINUTE, AFTER WHICH WAS ADDED TWO AND A HALF UNITS KLENOW."

Q. AND THEN WE TALKED IN SOME DETAIL, FOR EXAMPLE, ABOUT EXAMPLE 10.

DOES EXAMPLE 10 HAVE A -- AN INDICATION OF THE ANNEALING TIME?

A. IN EXAMPLE 10, LET'S SEE WHERE IT SAYS THAT.

IT SAYS THEY WERE HEATED TO A HUNDRED DEGREES C FOR ONE MINUTE, COOLED TO 25 DEGREES C FOR ONE MINUTE, AND TREATED WITH TWO UNITS OF KLENOW FRAGMENT FOR TWO MINUTES.

Q. AND THEN ONE LAST THING:

MR. FIGG SHOWED YOU ANOTHER PATENT THAT YOU AND SOME OF THE OTHER SCIENTISTS AT CETUS HAD -- HAD OBTAINED -- HAVE OBTAINED CONSIDERING -- CONCERNING THE LABELING OF OLIGONUCLEOTIDES.

WOULD YOU LOOK AT FIGURE 11 IN COLUMN 26 OF THE '202 PATENT, PLEASE.

(PAUSE IN PROCEEDINGS)

THE WITNESS: COLUMN . . .

Q. (BY MR. PASAHOW) 26, EXAMPLE 11.

A. 26.

(PAUSE IN PROCEEDINGS)

THE WITNESS: YEAH. I THINK THAT PATENT WAS NOT JUST FOR LABELING OLIGONUCLEOTIDES. IT WAS LABELING ALL KINDS OF DNA, BUT THAT I DON'T THINK IS GERMANE TO THIS -- I MEAN, THAT PATENT IS REFERENCED IN THIS -- IN THIS PATENT.

Q. (BY MR. PASAHOW) AND IS IT SPECIFICALLY REFERENCED THERE IN EXAMPLE 11 AROUND LINE 50?

A. YES. IT SAYS:

"AS DESCRIBED IN U.S. PATENT NUMBER FOUR MILLION FIVE HUNDRED" SO ON "ISSUED APRIL 15TH . . . TO K. MULLIS, ET AL., THE DISCLOSURE OF WHICH IS INCORPORATED HEREIN BY REFERENCE."

SO WE -- WE SENT THAT PATENT TO THEM, OR WE TOLD THEM HOW TO GET IT. I GUESS WE PROBABLY SENT THEM A COPY OF IT WHILE WE WERE FILING THIS -- THIS PATENT.

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

THE COURT: THANK YOU.

MR. FIGG.

(PAUSE IN PROCEEDINGS)

MR. PASAHOW: YOUR HONOR, THIS DRAWING MR. -- DR. MULLIS DID OF THE VARIOUS STRUCTURES COMING DOWN TO THE PARTICULAR PIECE NEEDS TO BE MARKED.

THE COURT: YES. DEFENDANT'S NEXT IN ORDER.

THE CLERK: DEFENDANT'S B-255 MARKED FOR IDENTIFICATION

ONLY.

(DEFENDANT'S EXHIBIT B-255
MARKED FOR IDENTIFICATION)

RECROSS-EXAMINATION

BY MR. FIGG:

Q. NOW, DR. MULLIS, YOU READ FROM THE VERY FIRST PARAGRAPH OF YOUR PATENT AND . . . INDICATED THAT "AMPLIFYING" MEANS LARGE COMPARED WHAT -- TO WHAT WAS ORIGINALLY PRESENT.

BUT, AGAIN, AT THE RISK OF BEING REPETITIVE, CLAIM 1 COVERS TWO CYCLES. WE'VE ESTABLISHED THAT; HAVEN'T WE?

A. AT -- YEAH, IT IS REPETITIVE, MR. FIGG, BUT, YES, WE HAVE ESTABLISHED THAT.

Q. AND YOU'VE ALREADY TOLD ME THAT THE REACTION IS EXPONENTIAL IF THE AMOUNT OF PRODUCT FORMED EXCEEDS THE AMOUNT OF DEGRADATION.

DO YOU RECALL THAT?

A. DO I RECALL TELLING YOU THAT --

Q. YES, DURING --

A. -- THAT -- THAT THE PROCESS IS EXPONENTIAL . . .

COULD YOU STATE THAT QUESTION AGAIN?

Q. WELL, I'M JUST TRYING TO ESTABLISH THAT, WHEN YOU AND I WERE CHATTING YESTERDAY DURING CROSS-EXAMINATION, I BELIEVE YOU CONFIRMED THAT A REACTION IS EXPONENTIAL IF IT FORMS PRODUCT AT A RATE THAT EXCEEDS DEGRADATION.

A. I NEVER SAID IT EXACTLY THAT WAY, UNLESS YOU'VE JUST TAKEN

THAT LINE OUT OF CONTEXT.

A PROCESS IS EXPONENTIAL IF IT HAS A CHARACTER ABOUT IT SUCH THAT THE AMOUNT THAT IS -- THAT IS PRODUCED IN ANY ONE CYCLE IS DEPENDENT ON -- ON THE AMOUNT THAT WAS PRESENT IN THE LAST CYCLE, AND THAT'S AN EXPONENTIAL PROCESS.

IT COULD BE THAT AN EXPONENTIAL PROCESS IS VERY INEFFICIENT AND ONLY PRODUCES A VERY SMALL AMOUNT OF PRODUCT.

Q. OKAY.

A. I --

Q. THAT'S WHAT I WAS TRYING TO SAY.

A. I THINK THAT'S BEEN SO CLEARLY BROUGHT OUT IN THIS TRIAL, WE DON'T NEED TO BORE EVERYBODY TO DEATH.

Q. I WASN'T TRYING TO BORE ANYONE, NOR WAS I TRYING TO CHANGE WHAT YOU'D SAID EARLIER.

BUT IF YOU HAVE TWO CYCLES OF A VERY LOW EFFICIENCY REACTION, LET'S SAY YOU HAVE A REACTION THAT IS TEN PERCENT EFFICIENT, HOW MUCH MORE DNA WILL YOU HAVE AFTER THE SECOND CYCLE THAN YOU STARTED WITH?

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) YOU'LL HAVE TEN PERCENT MORE; WON'T YOU?

A. RIGHT, AND . . . I -- I -- WE KEEP TALKING ABOUT -- THE PROCESS -- OKAY.

THE PROCESS THAT THIS INVENTION IS, IS -- IS -- IT'S COMPRISED OF. I MEAN, THESE -- WHAT THE CLAIM IS SAYING, IT STATES IT RATHER -- I MEAN, IT'S -- IT'S EXPECTED THAT YOU'RE

GOING TO DO A LOT MORE THAN TWO CYCLES.

IT SAYS THAT: "THE PRESENT INVENTION RELATES TO A PROCESS" -- OKAY -- "FOR PRODUCING ANY PARTICULAR NUCLEIC ACID SEQUENCE FROM A GIVEN SEQUENCE OF DNA . . . IN AMOUNTS WHICH ARE LARGE COMPARED TO THE AMOUNT INITIALLY PRESENT."

AND IT GOES ON AND SAYS: "YOU ACCOMPLISH THE AMPLIFICATION OF THIS WITH A CYCLIC PROCESS."

A REPETITIVE PROCESS.

NOW, IT DESCRIBED -- IN THE CLAIMS, IT SAYS THAT THE PROCESS COMPRISES; RIGHT? THAT MEANS THE PROCESS -- IF THE PROCESS COMPRISES THESE TWO CYCLES, IT MEANS IT HAS THOSE IN IT AS A PART OF IT; RIGHT? IT DOESN'T SAY THAT IT'S JUST THOSE TWO CYCLES. NOWHERE IN THIS PATENT DOES IT SAY IT'S JUST THOSE TWO CYCLES.

IT COMPRISES IT. AND YOU COULD, IN FACT, . . . FALL UNDER THIS CLAIM BY JUST DOING TWO CYCLES, BUT IT'S CERTAINLY NOT RECOMMENDED ANYWHERE IN THIS PATENT THAT WE DO THAT.

Q. WELL, I'M NOT FOCUSING ON WHAT'S RECOMMENDED. I'M FOCUSING ON WHAT YOUR CLAIM COVERS.

AND IT WOULD COVER DOING A REACTION INVOLVING TWO CYCLES WITH TEN PERCENT EFFICIENCY WHERE YOU WOULD END UP WITH TEN PERCENT MORE DNA THAN YOU STARTED WITH; ISN'T THAT CORRECT, DR. MULLIS?

A. IF YOU -- IF, IN FACT, IN THAT REACTION THE PRODUCTS OF THE

EXTENSION OF THE PRIMERS FROM THE FIRST CYCLE WAS USED AS A TEMPLATE FOR THE PRIMERS IN THE SECOND CYCLE.

WE'VE ALL GOT IT MEMORIZED.

Q. THAT'S RIGHT.

AND IF YOU GOT TEN PERCENT MORE PRODUCT THAN YOU STARTED WITH, AND IT MET THAT CONDITION THAT YOU JUST RECITED, IT WOULD BE COVERED BY THIS CLAIM.

A. THAT'S CORRECT, MR. FIGG.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) NOW, YOU WENT THROUGH A -- THE FIGURE 4 OF THE '202 PATENT WITH MR. PASAHOW, AND YOU DESCRIBED A SCHEMATIC ILLUSTRATION THERE THAT SPANNED THREE PAGES.

THAT ILLUSTRATION ILLUSTRATED A REACTION IN WHICH YOU WERE AMPLIFYING A SEQUENCE THAT WAS CONTAINED WITHIN A LONGER SEQUENCE; ISN'T THAT CORRECT?

A. THAT IS CORRECT.

Q. AND THAT FACT IS -- THE FACT THAT IT WAS A SEQUENCE CONTAINED WITHIN A LONGER SEQUENCE IS THE REASON THAT, IN THAT SCHEMATIC ILLUSTRATION, YOU HAD TO SHOW LONG PRODUCTS AND SHORT PRODUCTS AND THE ACCUMULATION OF THE SHORT PRODUCTS BOUNDED BY THE PRIMERS BEGINNING WITH THE THIRD CYCLE.

A. THAT IS . . . IT -- IT DOES, IN FACT, REQUIRE A LITTLE MORE EXPLANATION THAN SOME -- SOME . . . SIMPLIFIED SUBSET OF ALL THE POSSIBLE PCR REACTIONS.

THAT DIAGRAM WAS MADE TO DESCRIBE ALL OF THEM.

Q. WELL, IF YOU RAN THE PCR REACTION ILLUSTRATED IN EXHIBIT A-184, WOULD YOU --

A. WE HAVE NOT HAD ANY TESTIMONY TO THE EFFECT THAT THAT ILLUSTRATES A PCR REACTION.

Q. WELL, I THINK THE RECORD WILL SPEAK FOR ITSELF, DR. MULLIS, BUT --

A. OKAY.

Q. IF ONE CARRIED OUT THIS REACTION AS ILLUSTRATED HERE, YOU'RE NOT GOING TO GET ANY OF THOSE LONG PRODUCTS; ARE YOU?

A. THE REACTION THAT'S ILLUSTRATED THERE IS -- IS -- IS LIKE -- IT'S -- IT LOOKS LIKE YOU'RE GOING TO EXTEND ONE PRIMER ON ONE SINGLE-STRANDED TEMPLATE GETTING A DOUBLE-STRANDED PRODUCT AND THEN YOU'RE GOING TO EXTEND TWO PRIMERS ON THAT DOUBLE-STRANDED PRODUCT, AND YOU'RE GOING TO DO IT ONCE.

IT DOESN'T INDICATE THAT YOU'RE GOING TO DO IT TWICE. IT DOESN'T INDICATE THAT YOU'RE GOING TO REPEAT IT. IT'S EXACTLY WHAT I WAS DOING, AND IT WAS JUST FOR MY OWN PURPOSES THAT I PUT THAT DOWN IN MY NOTEBOOK. I DIDN'T MAKE THAT UP, AS HAS BEEN CLEARLY TESTIFIED TO, TO ILLUSTRATE A PCR REACTION.

Q. DR. MULLIS, DIDN'T YOU CALL THIS REACTION PCR 117 IN YOUR NOTEBOOK?

A. I -- I'M NOT SURE WHAT I CALLED IT. DOES IT SAY THAT?

Q. I THINK IT DOES. IF YOU'D LOOK AT PAGES 117 AND 118 OF YOUR NOTEBOOK.

A. WHICH NOTEBOOK?

Q. I THINK IT'S 1365.

MR. PASAHOW: I THINK I MAY HAVE TAKEN THAT FROM HIM.

THE WITNESS: IS THAT IT?

(PAUSE IN PROCEEDINGS)

THE WITNESS: THERE'S QUITE A BIT OF INFORMATION -- THERE ARE QUITE A BIT OF THINGS ON THE PAGE WHERE IT SAYS PCR 117, AND THAT IS ONE OF THE THINGS ON THERE.

BUT . . . THAT -- THAT LITTLE DIAGRAM, YOU CAN SEE, IS CUT OUT. IT'S THE OUTPUT FROM A COMPUTER FILE THAT I HAD, AND THE NAME OF THE COMPUTER FILE WAS KM 31, WHICH WAS THE NAME OF THE 58-BASE LONG SINGLE-STRANDED PRIMER OR SINGLE-STRANDED TEMPLATE AS IT WAS USED IN THIS REACTION THAT IS ILLUSTRATED AT THE TOP OF THAT FIGURE.

YOU SEE WHERE IT SAYS "KM 31 DUE JUNE 1984?" THAT'S THE NAME OF THE FILE THAT THAT THING CAME OUT OF. THAT'S WHAT THE NAME OF THAT DIAGRAM WAS.

THERE ARE OTHER DIAGRAMS ON THIS PAGE. THERE'S A -- THERE'S A WHOLE PROCEDURE ON THIS PAGE, AND PCR 117 REFERS TO EVERYTHING ON THIS PAGE AND PROBABLY ON PAGES AFTER THAT IN WHICH THINGS WERE ANALYZED.

AND IT DESCRIBES A PCR REACTION, BUT THAT PARTICULAR DIAGRAM, WHICH YOU'VE PULLED OUT OF CONTEXT, IS JUST A -- IS MY WAY OF DESCRIBING WHAT KM 31 WAS BEING SYNTHESIZED FOR.

(PAUSE IN PROCEEDINGS)

THE WITNESS: YOU SEE HOW IT WAS CUT OUT AND PASTED IN

THERE?

Q. (BY MR. FIGG) IN FACT, WHAT WAS CUT OUT AND PASTED IN THERE WAS EXACTLY WHAT'S PRINTED AT THE TOP OF THIS PAGE.

A. THAT'S RIGHT. IT WAS -- IT WAS THE UPPER LEFT-HAND CORNER OF THIS PAGE.

AND RIGHT UNDER IT, THERE'S ANOTHER THING. IT SAYS "KM 31 DNA." THAT DOESN'T DESCRIBE A PCR REACTION, EITHER, MR. FIGG. THAT JUST DESCRIBES THE MOLECULAR WEIGHT, THE MOLAR EXTINCTION, THE MICROGRAMS PER OD, THE PICOMOLES PER OD, ET CETERA, ABOUT KM 31.

THIS OTHER DIAGRAM OVER HERE, WHICH YOU'VE SEEMED TO LEFT OFF YOUR CHART, ALSO ON THE SAME PAGE, PCR 117, DESCRIBES A LOT OF VERY COMPLICATED STUFF, ALL OF WHICH WAS RELATED TO PCR 117, WHICH IS THE REACTION DESCRIBED ON THIS PAGE BELOW ALL THAT STUFF, AND ON THE NEXT PAGE WHEN I WAS ANALYZING IT.

I MEAN, THERE'S A LOT OF THINGS ON THAT PAGE THAT DON'T DESCRIBE PCR AT ALL.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DR. MULLIS, NOTWITHSTANDING ALL OF THAT, IF . . .

I THINK WE AGREED DURING YOUR CROSS-EXAMINATION . . . THAT YOU CAN BEGIN THIS REACTION WITH A DISCRETE DNA MOLECULE WHERE THE PRIMERS ANNEAL FLUSH WITH THE ENDS OF THE TWO TEMPLATE STRANDS; DIDN'T WE?

A. YES, WE DID.

Q. MY QUESTION IS SIMPLY THIS:

IF YOU ILLUSTRATED THAT KIND OF A REACTION, IT WOULD NOT CONTAIN ALL OF THE LONG PRODUCTS AND THE OTHER THINGS THAT YOU WERE ILLUSTRATING IN FIGURE 4 OF YOUR PATENT; WOULD IT? YOU WOULD NOT FORM LONG PRODUCTS IF YOU AMPLIFIED THAT KIND OF A SEQUENCE; IS THAT CORRECT?

A. ARE YOU ASKING ME TO ILLUSTRATE THAT FOR YOU RIGHT NOW AND SEE IF IT DOES OR DOES NOT, OR --

Q. NO, SIR. I'M SIMPLY --

A. -- OR IF I ILLUSTRATED IT?

Q. I'M SIMPLY ASKING YOU WHETHER OR NOT IT IS CORRECT THAT, IF YOU ILLUSTRATED THAT REACTION WHERE YOU'RE STARTING WITH A DISCRETE MOLECULE AS THE TARGET, THAT YOU WOULDN'T SHOW ANY LONG PRODUCTS ON THAT ILLUSTRATION; WOULD YOU?

A. NO, BUT IF I ILLUSTRATED THAT REACTION, AS COVERED BY THESE CLAIMS, I WOULD CLEARLY INDICATE THAT THE PRODUCTS OF THE FIRST CYCLE OF THE REACTION IN FACT SERVED AS TEMPLATES FOR THE PRIMERS DURING THE SECOND CYCLE OF THE REACTION, AND SO FORTH.

I -- I WOULD NOT HAVE ILLUSTRATED IT THAT WAY. I HAVE TOLD YOU I DIDN'T ILLUSTRATE IT THAT WAY, AND I -- I MEAN, ASK ME TO ILLUSTRATE IT RIGHT HERE IN THE COURTROOM AND YOU'LL SEE THAT IT DOESN'T LOOK LIKE YOUR LITTLE PICTURE THERE.

Q. DR. MULLIS, I SIMPLY WANTED YOU TO CONFIRM THAT NO LONG PRODUCTS WOULD SHOW UP ON THAT KIND OF AN ILLUSTRATION, AND I THINK YOU AGREE WITH ME THAT THAT IS SO.

A. I CERTAINLY AGREE WITH YOU, MR. FIGG, ON THAT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DR. MULLIS, DO YOU SEE THAT WE HAD MARKED THIS PAGE FROM YOUR NOTEBOOK OR -- EXCUSE ME. THIS WAS NOT A PAGE FROM YOUR NOTEBOOK. THIS WAS FROM ANOTHER DOCUMENT THAT YOU PRODUCED TO US.

BUT WE MARKED THAT DURING YOUR DEPOSITION AS DEPOSITION EXHIBIT 144?

A. IT LOOKS LIKE YOU DID MARK IT THAT WAY.

Q. OKAY.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) AND DO YOU RECALL THAT I ASKED YOU DURING YOUR DEPOSITION --

MR. PASAHOW: EXCUSE ME, YOUR HONOR. COULD WE HAVE A PAGE AND LINE REFERENCE?

THE COURT: YES.

MR. FIGG: PAGE 282, LINE 7.

Q. DO YOU RECALL THAT I ASKED YOU DURING YOUR DEPOSITION:

"AM I CORRECT THAT THE REACTION ILLUSTRATED ON EXHIBIT 184 IN THE PART OF THE ILLUSTRATION BELOW THE DOTTED LINE IS A PCR AMPLI -- PCR REACTION FOR AMPLIFYING THAT DISCRETE 58-BASE PAIR SEQUENCE?"

AND YOU ANSWERED: "YES, THE ONE THAT'S ILLUSTRATED THERE IS. IT'S NOT EXACTLY WHAT I DID ON PAGE 109 BECAUSE I JUST DID THE FIRST STEP."

AND I FOLLOWED UP AND I SAID: "I UNDERSTAND, BUT THIS IS A PCR REACTION."

AND YOU ANSWERED: "THAT IS A PCR REACTION, STARTING WITH SINGLE-STRANDED DNA SYNTHETIC TEMPLATE."

DO YOU RECALL THAT TESTIMONY?

A. I DO. IT SEEMS LIKE I'M SAYING PRETTY MUCH THE SAME THING NOW.

I'M SAYING THAT'S NOT EVERYTHING I DID ON P -- THE EXPERIMENT ENTITLED PCR 117, ALTHOUGH YOU SAID THERE PAGE 109. AND THAT WAS ANOTHER PCR REACTION CALLED PCR 105, I THINK.

WE WERE LOOKING AT -- WE WERE LOOKING THROUGH MY NOTEBOOK JUST LIKE WE ARE NOW, AND YOU WERE POINTING TO THAT THING JUST LIKE WE ARE NOW, AND I WAS TELLING YOU EXACTLY THE SAME THING I'M TELLING YOU NOW: THAT IS JUST A PART OF THE EXPERIMENT THAT I WAS PERFORMING.

AND YOU AS USUAL JUST KEPT COMING BACK AND SAID, "BUT IS IT? ARE YOU SURE IT'S NOT, DOCTOR?" AND SO FORTH AND SO ON.

AND THEN YOU SLIPPED IN THIS LITTLE -- YOU KNOW, PULL THAT OUT OF CONTEXT, AND YOU'RE TRYING TO MAKE IT LOOK LIKE THAT, IN FACT, IS PCR BUT, MR. FIGG, IT IS NOT PCR. I TOLD YOU IT WASN'T PCR AND I EXPLAINED TO YOU WHY.

I MEAN --

Q. DOCTOR, I DON'T KNOW HOW YOUR ANSWER COULD HAVE BEEN ANY MORE CLEAR.

A. READ IT AGAIN.

Q. I ASKED YOU:

"I UNDERSTAND. BUT IS THIS A PCR REACTION?"

YOUR COMPLETE ANSWER TO THAT QUESTION WAS:

"THAT IS A PCR REACTION, STARTING WITH A SINGLE-STRANDED DNA SYNTHETIC TEMPLATE."

A. OKAY.

Q. NOW, THEN, YOU --

A. GO BACK AND READ THE WHOLE THING AGAIN FOR US, THEN.

I MEAN, I -- YOU STARTED IN THE MIDDLE THAT TIME. THE PART I'D LIKE YOU TO READ IS WHERE IT SAYS THAT IS, BUT IT'S ONLY A PART OF IT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DO YOU STILL HAVE YOUR NOTEBOOK NUMBER 1,000 THERE, DR. MULLIS?

A. YES, I DO.

Q. NOW, YOU INDICATED TO MR. PASAHOW THAT IN THE REACTION DESCRIBED ON PAGE 173, YOU COOLED THE REACTION AFTER DENATURATION. YOU COOLED THE DNA TO 32 DEGREES. IS THAT WHAT YOU TOLD HIM?

A. THAT I . . . I TOLD MR. PASAHOW THAT I --

Q. YES.

A. -- COOLED IT TO 32. I THINK I READ IT RIGHT THERE.

Q. IT'S ON PAGE 175, I THINK.

A. OKAY. BY THE WAY, HERE ON PAGE 173 IS ANOTHER DIAGRAM OF PCR REACTION. YOU MIGHT TAKE A LOOK AT IT SOMETIME. THAT'S AN

ABBREVIATED FORM FOR MY OWN PERSONAL USE.

Q. YEAH. THERE ARE A LOT OF THEM IN THERE.

A. UH-HUH.

Q. BUT THE CURRENT QUESTION IS:

YOU COOLED THIS REACTION TO 32 DEGREES?

A. YES.

Q. AND YOU DID THAT BY PLACING IT IN A WATER BATH. YOU DIDN'T JUST LET IT COOL AT ROOM TEMPERATURE DOWN TO 32 DEGREES.

A. IT SAYS, "COOL IN WATER BATH TO 32 DEGREES." IT WOULDN'T COOL TO 32 AT ROOM TEMPERATURE. ROOM TEMPERATURE IS GENERALLY 23.

Q. YEAH, UNLESS IT WAS A PRETTY WARM ROOM.

A. A VERY WARM ROOM, YEAH.

Q. AM I CORRECT THAT THE MELTING TEMPERATURES OF THESE TWO PRIMERS THAT YOU WERE USING IN THIS EXPERIMENT ARE BOTH HIGHER THAN 32 DEGREES?

A. YES, THEY ARE. APPROXIMATELY 25 DEGREES HIGHER.

Q. YEAH. ONE IS 54 DEGREES, 54.6, AND THE OTHER ONE IS 54 POINT -- 51.7?

A. THAT'S CORRECT, UH-HUH.

Q. OKAY. SO WHEN YOU COOLED, YOU -- YOU COOLED IN A WATER BATH TO A POINT THAT WAS BELOW THE MELTING TEMPERATURES OF THE OLIGOS THAT YOU WERE USING.

A. YES.

MR. FIGG: OKAY. NO FURTHER QUESTIONS, YOUR HONOR.

10

THE COURT: THANK YOU.

DR. MULLIS, YOU MAY STEP DOWN, FINALLY.

THE WITNESS: WELL, IT'S BEEN AN ENJOYABLE PROCEDURE.

(LAUGHTER)

(WITNESS EXCUSED)

MR. PASAHOW: OUR NEXT WITNESS IS GOING TO BE HANDLED BY MR. LEWIS.

THE COURT: OKAY. DO WE HAVE SOME EXHIBITS WE NEED TO TAKE CARE OF?

MR. FIGG: OH, YES. THANK YOU, YOUR HONOR.

(PAUSE IN PROCEEDINGS)

MR. FIGG: YOUR HONOR, WE OFFER EXHIBIT A-184, WHICH IS THE POSTER ON THE KM 31 EXPERIMENT.

MR. PASAHOW: NO OBJECTION.

(PLAINTIFF'S EXHIBIT A-184 RECEIVED IN EVIDENCE)

MR. FIGG: A-185, WHICH IS THE . . . EXAMPLES OF THE '202 PATENT, DIAGRAMS. THE OVERLAP EXAMPLES.

(PAUSE IN PROCEEDINGS)

MR. PASAHOW: OH, THE TWO PRIMERS?

MR. FIGG: YEAH.

MR. PASAHOW: NO OBJECTION.

(PLAINTIFF'S EXHIBIT A-185 RECEIVED IN EVIDENCE)

MR. FIGG: A-23, WHICH IS THE ABSTRACT.

MR. PASAHOW: THE ARTICLE?

MR. FIGG: YEAH, THE ABSTRACT.

MR. PASAHOW: NO -- NO OBJECTION.

(PLAINTIFF'S EXHIBIT A-23 RECEIVED IN EVIDENCE)

MR. FIGG: A-162, WHICH IS THE CURRENT COMMUNICATIONS ARTICLE.

MR. PASAHOW: NO OBJECTION. I THOUGHT THEY WERE IN EVIDENCE.

MR. FIGG: I DON'T THINK THEY EVER WERE.

THE CLERK: (SHAKING HEAD.)

(PAUSE IN PROCEEDINGS)

MR. FIGG: I'M SORRY. EXHIBIT A-162 WAS THE POSTER EXCERPT FROM THE CURRENT COMMUNICATIONS.

MR. PASAHOW: NO OBJECTION.

(PLAINTIFF'S EXHIBIT A-162 RECEIVED IN EVIDENCE)

MR. FIGG: AND A-24 IS THE ENTIRE ARTICLE, CURRENT COMMUNICATIONS.

MR. PASAHOW: NO OBJECTION TO THAT, EITHER.

MR. FIGG: OKAY.

(PLAINTIFF'S EXHIBIT A-24 RECEIVED IN EVIDENCE)

THE COURT: OKAY. THEN THEY'RE ALL ADMITTED.

AND YOU HAVE YOURS TAKEN CARE OF, MR. PASAHOW? HAVE WE