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VOLUME 6
PAGES 705 - 871

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
WEDNESDAY, JANUARY 16, 1991

APPEARANCES:

FOR PLAINTIFF:

ROTHWELL, FIGG, ERNST & KURZ
1700 K STREET, N.W.
SUITE 800
WASHINGTON, D.C. 20006

BY: E. ANTHONY FIGG, ESQ.
CELINE M. JIMINEZ, ESQ.
RAYMOND A. KURZ, ESQ.
BART G. NEWLAND, ESQ.

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

BY: GEORGE A. FRANK, ESQ
ROSEANNE R. DUFFY, ESQ.

(APPEARANCES CONTINUED ON NEXT PAGE)

REPORTED BY: CANDACE L. FRANCIS, CSR, CP, CM
JAMES YEOMANS, CSR
OFFICIAL REPORTERS, USDC

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APPEARANCES (CONTINUED):

FOR PLAINTIFF (CONTINUED):	PILLSBURY, MADISON & SUTRO 225 BUSH STREET BOX 7880 SAN FRANCISCO, CALIFORNIA 94104 BY: CLEMENT GLENN, ESQ.
FOR DEFENDANT:	MC CUTCHEN, DOYLE, BROWN & ENERSEN THREE EMBARCADERO CENTER SAN FRANCISCO, CALIFORNIA 94111 BY: LYNN H. PASAHOW, ESQ. JAMES B. LEWIS, ESQ. NINA SREJOVIC, ESQ. CETUS CORPORATION 1400-53RD STREET EMERYVILLE, CALIFORNIA 94608 BY: PETER D. STAPLE, ESQ.

I N D E X

MONDAY, JANUARY 16, 1991 8:15 A.M.

(PROCEEDINGS HELD IN OPEN COURT, JURY PRESENT:)

THE COURT: GOOD MORNING.

GOOD MORNING, LADIES AND GENTLEMEN.

MR. FIGG: GOOD MORNING, YOUR HONOR.

THE COURT: YOU MISSED ALL THE EXCITEMENT YESTERDAY, EXCEPT FOR MR. CALLIS WHO MANAGED TO GET THROUGH THE WHOLE THING AND SHOWED UP OUTSIDE MY CHAMBERS DOOR.

AT ANY RATE, I TRUST WE'LL BE ABLE TO FINISH THIS WITHOUT ANY SUCH FURTHER EVENTS OR DISRUPTIONS.

MR. FIGG: THANK YOU, YOUR HONOR.

THE COURT: YOU MAY CONTINUE.

BY THIS TIME HAVE YOU SHORTENED IT OR HAVE YOU THOUGHT OF EVEN MORE?

MR. FIGG: I THINK WE'RE STREAM LINING THINGS, YOUR HONOR.

THE COURT: GOOD.

ROBERT BRUCE WALLACE, PLAINTIFF'S WITNESS, PREVIOUSLY SWORN RESUMED

DIRECT EXAMINATION RESUMED

BY MR. FIGG:

Q. GOOD MORNING, DR. WALLACE.

A. GOOD MORNING, MR. FIGG.

Q. AT THE END OF OUR SESSION THE DAY BEFORE YESTERDAY YOU HAD

JUST FINISHED TALKING ABOUT CLAIM 19 AND THERE'S ONE CLAIM REMAINING IN ISSUE IN THE '202 PATENT THAT I WOULD LIKE FOR YOU TO DISCUSS, AND THAT IS CLAIM 20. CLAIM 20 READS AS FOLLOWS:

"THE PROCESS OF CLAIM 19, WHEREIN STEPS D AND C ARE REPEATED AT LEAST ONCE."

DO YOU HAVE AN OPINION AS TO WHETHER THE PROCESS CLAIMED BY CLAIM 20 IS DESCRIBED IN THE KLEPPE PAPER, THE KHORANA NSF GRANT APPLICATION AND THE PANET PAPER?

A. YES, I DO.

Q. WHY DON'T YOU JUST BRIEFLY RECAP CLAIM 19, BECAUSE CLAIM 20 IS DEPENDENT ON THAT.

MAY HE COME DOWN, YOUR HONOR?

THE COURT: YES. SURELY.

THE WITNESS: I JUST WANTED TO RECAP FOR THE JURY THE PROCESS OF CLAIM 19, WHICH IS SLIGHTLY DIFFERENT THAN CLAIM 1 BECAUSE IT SPELLS OUT FOUR STEPS.

THE FIRST STEP IS SEPERATING THE STRANDS OF THE DNA BY PHYSICAL, CHEMICAL OR ENZYMATIC MEANS: THAT IS THE PROCESS OF SEPARATING THE DOUBLE STRANDS DNA, TREATING THE SINGLE STRANDS OF OLIGONUCLEOTIDE PRIMERS FROM THE MOLAR EXCESS, WHICH IS THE DIVIDING PRIMER STEP.

SEPERATING AND DOING THE PRIMER EXTENSION REACTION, SO THAT'S THE FIRST ROUND. SEPARATING THE PRIMER EXTENSION PRODUCTS FROM THE TEMPLATES IN WHICH THEY'RE SYNTHESIZED TO PRODUCE SINGLE STRANDED MOLECULES, THAT'S SEPERATING THE STRANDS

OF THE NEWLY SYNTHESIZED PRIMER EXTENSION PRODUCTS. THEN TREATING THE SINGLE STRAND MOLECULES GENERATED FROM STEP 2 WITH TWO PRIMERS IN MOLAR EXCESS AND DOING ANOTHER ROUND.

SO THIS DENATURING FIRST ROUND OF PRIMER EXTENSION, DENATURING SECOND ROUND OF PRIMER EXTENSION. AND AS YOU'VE SEEN IN THE NSF GRANT APPLICATION, DENATURING PRIMER EXTENSION OR REPAIR REPLICATION, AS DR. KHORANA'S LAB CALLED IT, THEN REPEATING THE CYCLE.

CLAIM 20 SIMPLY SAYS REPEATING THE LAST TWO STEPS AT LEAST ONCE. SO WE'VE GONE THROUGH TWO ROUNDS OF CLAIM 19, CLAIM 20 DOES A THIRD ROUND, A MINIMUM OF THREE ROUNDS.

AND THE NSF GRANT APPLICATION, FOR EXAMPLE, SAYS REPEAT THE SATURATION AND THE WHOLE CYCLE AND INDICATES YOU COULD REPEAT THIS CYCLE, REPEAT IT AND RE-REPEAT IT. SO, YES, I DO BELIEVE CLAIM 20 IS TAUGHT BY THE THREE PRIOR ART REFERENCES WE'VE BEEN TALKING ABOUT.

Q. (BY MR. FIGG) DR. WALLACE, I BELIEVE YOU EXPRESSED THE OPINION THAT A PERSON OF ORDINARY SKILL IN THE ART IN 1984 WOULD HAVE BEEN ABLE TO FOLLOW THE TEACHINGS OF THE VARIOUS PIECES OF PRIOR ART FROM DR. KHORANA'S LAB AND SUCCESSFULLY ACCOMPLISH THAT PROCESS AND THE PROCESS COVERED BY CLAIM 1; IS THAT CORRECT?

A. YES.

Q. ARE YOU FAMILIAR WITH ANY -- ANY CORRESPONDENCE THAT YOU WOULD BELIEVE CONFIRMS OR RELATES TO THAT OPINION?

A. YES, I'M AWARE OF AN INTERNAL MEMO THAT WAS WRITTEN BY DOCTOR HENRY ERLICH AT THE CETUS CORPORATION, WHICH WAS BASICALLY A MEMO TO SCIENTISTS WITHIN CETUS DISCUSSING PARTICULAR PUBLICATION WHICH WAS CALLED THE FALOONA, MULLIS MANUSCRIPT.

Q. DOCTOR, I'LL HAND YOU A COPY OF A DOCUMENT THAT'S BEEN MARKED AS . . . SORRY, YOUR HONOR, THERE'S A STAMP RIGHT OVER THE EXHIBIT NUMBER. THAT'S BEEN MARKED AS EXHIBIT A-25.

IS THIS THE MEMO YOU'RE REFERRING TO?

A. YES, IT IS.

Q. HOW DO YOU BELIEVE THAT MEMO RELATES TO THIS QUESTION OF WHETHER A SKILLED PERSON COULD HAVE PRACTICED THIS PROCESS IN 1984?

A. WELL, IN THE -- IN THIS MEMO DOCTOR ERLICH MAKES THE STATEMENT:

"ONCE THE FUNDAMENTAL PRINCIPLE OF PCR HAS BEEN DISCLOSED, ANY GOOD MOLECULAR BIOLOGIST WILL BE AWARE OF THE RELEVANT PARAMETERS TO EXPLORE. FOR EXAMPLE, TIME OF INCUBATION, REAGENT, THAT IS PRIMERS, ENZYMES, CONCENTRATION, TEMPERATURE, LENGTH OF PRIMERS, ET CETERA, EVEN THE APPROACHES THAT ARE ONLY QUOTE 'SEMI-OBVIOUS' E.G. THE USE OF NESTED PRIMERS, WILL BE APPARENT EVENTUALLY."

SO I THINK THIS STATEMENT KIND OF REFLECTS WHAT I'VE BEEN TRYING TO SAY. ITS REALTY CONCEPT OF THE TWO PRIMERS AND

THEIR PRIMER EXTENSION PRODUCTS SERVING AS TEMPLATES FOR SUBSEQUENT ROUNDS OF PRIMER EXTENSION THAT WOULD -- THAT DR. ERLICH SEEMS TO BE TRYING TO EXPRESS HERE.

Q. IN YOUR OPINION, IS THE FUNDAMENTAL PRINCIPLE OF PCR DESCRIBED IN THE KLEPPE PAPER AND THE NSF GRANT AND THE PANET PAPER?

A. YES, ALL THOSE THREE PIECES OF PRIOR ART DESCRIBE THIS FUNDAMENTAL PRINCIPLE OF SEQUENTIAL ROUNDS OF PRIMER EXTENSION.

Q. DR. WALLACE, I'D NOW LIKE TO TURN TO A DISCUSSION OF THE OTHER PATENT IN ISSUE IN THIS CASE, THE 195 PATENT. HAND YOU A COPY OF EXHIBIT A-2.

DO YOU RECOGNIZE THAT AS THE PATENT THAT WE'VE BEEN CALLING THE 195 PATENT?

A. YES, I DO.

Q. DOCTOR, COULD YOU PROVIDE THE JURY WITH JUST A GENERAL OVERVIEW OF WHAT THAT PATENT COVERS?

A. WELL, THE '202 PATENT WAS A PROCESS FOR AMPLIFYING AND THE 195 PATENT IS A PROCESS FOR DETECTING NUCLEIC ACID SEQUENCES, I BELIEVE A PROCESS FOR DETECTING IN CLAIM 1. AND THE PATENT TAKES ADVANTAGE OF THE WHAT HAS BEEN CALLED THE PCR PROCESS, AND USES THAT PROCESS FOR AMPLIFYING DNA. AND THEN USES ANOTHER PROCESS CALLED HYBRIDIZATION FOR DETECTING WHETHER PARTICULAR SEQUENCES WERE PRESENT IN THE SAMPLE PRIOR TO THE AMPLIFICATION STEP.

Q. HAVE YOU COMPARED THE '195 PATENT WITH THE '202 PATENT?

A. YES, I HAVE.

Q. ARE THERE SIMILARITIES BETWEEN THOSE TWO PATENTS?

A. YES, A GREAT DEAL OF SIMILARITY BETWEEN THE '202 PATENT AND THE '195 PATENT.

Q. DR. WALLACE, WE PREPARED A BLOW UP OF CLAIM 1 OF THE '195 PATENT AND PERHAPS YOU COULD COME DOWN AND GO THROUGH THIS CLAIM WITH THE HELP OF SOME OF OUR EXHIBITS AND EXPLAIN HOW IT WORKS.

A. WELL, AGAIN, THIS LANGUAGE IS SORT OF STRANGE, BUT THIS IS THE CLAIM 1 OF THE '195 PATENT AND YOU'LL SEE IT'S BROKEN DOWN INTO STEPS A, B, C, D AND E, DIFFERENT FROM THE '202 PATENT WHERE THERE WERE ONLY A, B C. THAT STARTS OUT:

"A PROCESS FOR DETECTING THE PRESENCE OR ABSENCE OF AT LEAST ONE SPECIFIC NUCLEI ACID SEQUENCE IN A SAMPLE CONTAINING A NUCLEIC ACID OR MIXTURE OF NUCLEIC ACIDS, OR DISTINGUISHING BETWEEN TWO DIFFERENT SEQUENCES IN SAID SAMPLE, WHEREIN THE SAMPLE IS SUSPECTING OF CONTAINING SAID SEQUENCE OR SEQUENCES WHICH PROCESS COMPRISES."

SO YOU'RE BEGINNING IN THIS CLAIM WITH AT LEAST ONE SPECIFIC NUCLEIC ACID SEQUENCE AND ONE SPECIFIC NUCLEIC ACID SEQUENCE, COULD BE A DOUBLE STRANDED DNA MOLECULE AS SHOWN HERE.

STEP A SAYS:

"TREATING THE SAMPLE WITH ONE OLIGONUCLEOTIDE PRIMER FOR EACH STRAND OF EACH DIFFERENT SPECIFIC SEQUENCE, UNDER HYBRIDIZING CONDITIONS SUCH THAT FOR

EACH STRAND OF EACH DIFFERENT SEQUENCE TO WHICH AN OLIGONUCLEOTIDE PRIMER IS HYBRIDIZED AN EXTENSION PRODUCT OF EACH PRIMER IS SYNTHESIZED WHICH IS COMPLIMENTARY TO EACH NUCLEIC ACID SEQUENCE STRAND. WHEREIN SAID PRIMER OR PRIMERS ARE SELECTED SO AS TO BE SUFFICIENTLY COMPLIMENTARY TO EACH STRAND OF EACH SPECIFIC SEQUENCE TO HYBRIDIZE THEREWITH SUCH THAT THE EXTENSION PRODUCT SYNTHESIZED FROM ONE PRIMER, WHEN IT IS SEPARATED FROM ITS COMPLIMENT, CAN SERVE AS A TEMPLATE FOR SYNTHESIS OF THE EXTENSION PRODUCT OF THE OTHER PRIMER."

SO THIS IS A LONG DISCUSSION OF WHAT THE PRIMER SHOULD DO AND WHERE THEY SHOULD BE. IN ORDER TO SYNTHESIS THE EXTENSION PRODUCT YOU MUST FIRST DENATURE OR SEPARATE THE STRANDS, BIND THE APPROPRIATE PRIMERS AS SHOWN HERE AS YOU'RE VERY FAMILIAR WITH BY NOW, PRODUCE THE EXTENSION PRODUCT WITH THE ENZYME DNA POLYMERASE, FOR EXAMPLE.

BUT IT JUST SAYS PRODUCE EXTENSION PRODUCT AND AT THE END OF STEP A, THEN YOU WILL HAVE PRODUCED TWO MOLECULES FROM THE ONE DOUBLE STRANDED DNA MOLECULE, IF THAT'S WHAT YOU STARTED WITH.

"B, TREATING THE SAMPLE UNDER DENATURING CONDITIONS TO SEPARATE THE PRIMER EXTENSION PRODUCTS FROM THEIR TEMPLATES IF THE SEQUENCE OR SEQUENCES TO BE DETECTED ARE PRESENT."

THIS PART OF THE CLAIM IS IMPORTANT IN TWO WAYS: ONE IT'S THE NEXT STEP WHICH, OF COURSE, THE NEXT ROUND OF DENATURATION, BUT YOU NOTICE IT ALSO SAYS "IF THE SEQUENCE OR SEQUENCES TO BE DETECTED ARE PRESENT" SIMPLY BECAUSE IT'S POSSIBLE THAT THE SEQUENCES MIGHT NOT HAVE BEEN PRESENT AT ALL AT THE BEGINNING. SO YOU CAN -- YOU SEPARATE THEM, THE PRIMER EXTENSION PRODUCTS AS IT SAYS.

THEN C: "TREATING THE SAMPLE WITH OLIGONUCLEOTIDE PRIMERS SUCH THAT A PRIMER EXTENSION PRODUCT IS SYNTHESIZED USING EACH OF THE SINGLE STRANDS PRODUCED IN STEP B AS A TEMPLATE, RESULTING IN AMPLIFICATION OF THE SPECIFIC NUCLEIC ACID SEQUENCE OR SEQUENCES IF PRESENT."

SO YOU CAN BIND YOUR PRIMERS AGAIN TO THE PRODUCT OF STEP A AND AFTER DENATURATION BY STEP B TO PRODUCE ANOTHER ROUND OF PRIMER EXTENSION. SO YOU'VE GONE FROM ONE SEQUENCE TO TWO AND WITH THESE TWO STEPS YOU'VE GONE FROM TWO SEQUENCES TO FOUR.

STEP D SAYS: "ADDING TO THE PRODUCT OF STEP C A LABELED OLIGONUCLEOTIDE PROBE FOR EACH SEQUENCE BEING DETECTED CAPABLE OF HYBRIDIZING TO SAID SEQUENCE OR A MUTATION THEREOF.

FIRST I NEED TO EXPLAIN WHAT OLIGONUCLEOTIDE PROBE IS. WE MADE THIS PROBE RED BECAUSE OLIGONUCLEOTIDE PROBE IS ESSENTIALLY NOT DIFFERENT FROM AN OLIGNONUCLEOTIDE PRIMER. IT'S A PIECE, FOR EXAMPLE, SYNTHESIZED DNA, BUT IT'S A PROBE BECAUSE

IT'S LABELED IN SOME WAY.

IT IS REACTED WITH SOMETHING EITHER, FOR EXAMPLE, THE MOST COMMON WAY I THINK IS WITH RADIOACTIVITY, SO THAT THE MOLECULE ITSELF CAN BE DETECTED BY SOMETHING. SO IT'S A PROBE AND YOU'RE GOING TO REACT THE PRODUCT OF STEP C WITH A LABELED PROBE AND LABELED PROBES BEHAVE LIKE THE PRIMERS IN A SENSE THEY CAN BIND OR STICK ON THE PRODUCT AND THIS BINDING OR STICKING CAN BE DETECTED BECAUSE OF THE LABEL.

AND THEN STEP E:

"DETERMINING WHETHER SAID HYBRIDIZATION HAS OCCURRED." THIS BINDING OR STICKING IS CALLED HYBRIDIZATION.

Q. THANK YOU, DOCTOR.

I THINK WE HAVE THE VIDEO THAT PERHAPS YOU WANT TO STAY DOWN HERE WE'LL RUN THE VIDEO AND USE THE MONITOR THERE, GOING THROUGH THE PROCESS AGAIN.

A. SO WE'RE GOING TO GO THROUGH THE POLYMERASE CHAIN REACTION PROCESS STARTING WITH DUPLEX DNA STRAND OR DOUBLE STRANDED DNA. YOU MUST FIRST SEPARATE THE TWO STRANDS, FOR EXAMPLE, BY HEATING AND THEY COME APART, THOSE ARE CALLED DENATURED DNA STRANDS.

HERE YOU SEE A LAB WORKER PUTTING INTO A TEST TUBE PRIMERS AND THE PRIMERS UPON COOLING THEN WILL FIND THEIR COMPLIMENTARY SITE, THE REGIONS WHICH THEY STICK. SO THE PRIMERS ARE SAID TO ANNEAL TO THE TEMPLATES SUCH -- IN OTHER WORDS, STICKING TO THE TEMPLATES.

YOU ADD POLYMERASE AND NUCLEOTIDES AND YOU'LL RECALL

THAT THE POLYMERASE IS LITTLE MACHINE WHICH TAKES ITS DIRECTION FROM THE TEMPLATE SENDING THE PRIMER IN THIS DIRECTION ON BOTH STRANDS AND ACHIEVING A COPYING, COMPLETE COPYING OF THE TWO STRANDS SO THAT WHEN IT'S FINISHED COPYING YOU HAVE ACHIEVED A DOUBLING OF THE NUMBER OF TEMPLATES.

Q. WHERE ARE WE IN CLAIM 1 OF THE '195 PATENT?

A. WHAT WE'VE BASICALLY DONE IS COMPLETED STEP A. WE TREATED WITH THE OLIGNONUCLEOTIDE AND WITH APPROPRIATE PRIMERS AND ACHIEVED A DOUBLING BY PRIMER EXTENSION, TWO IDENTICAL DUPLEX STRANDS.

AND YOU REPEAT THE PROCESS YOU HAVE TO DO -- REMEMBER YOU HAVE TO DENATURE AND DO ANOTHER ROUND OF PRIMER EXTENSION. SO WE SEPARATE THE STRANDS. THE PRIMERS BIND UPON COOLING. THE POLYMERASE MAKES COPIES UNDER DIRECTION OF THE TEMPLATES THAT ARE PRESENT AND YOU'VE NOW ACHIEVED FOUR IDENTICAL DUPLEX STRANDS STARTING FROM ONE, NOW YOU'VE COMPLETED STEP C.

SO THIS IS THE TYPE DETECTION OF AMPLIFIED DNA WITH A LABELED PROBE. HERE YOU SEE THE -- FIRST I MUST EXPLAIN HOW YOU WOULD ACTUALLY DO THIS AND ONE WAY TO DO THIS WOULD BE TO TAKE THE PRODUCT OF STEP C AND WHAT YOU'LL SAY IMMOBILIZE, STICK IT TO SOMETHING WE CALL THAT SOMETHING A MEMBRANE, A SPECIAL PIECE OF MATERIAL WHICH DNA WILL STICK TO UNDER CERTAIN CONDITIONS.

SO YOU ACTUALLY STICK THE DNA TO THAT MEMBRANE. IN THIS CASE IT'S USING AN APPARATUS THAT'S CALLED A ACTUALLY CALLED A SLOT BLOCK APPARATUS. DOESN'T REALLY MATTER, IT'S A

WAIVE SUCKING A LITTLE BIT OF LIQUID THROUGH THESE HOLES ON TO THE MEMBRANE SO THE DNA STICKS IN A STRIPE ON THE MEMBRANE.

ONCE IT'S STUCK TO THE STRIPE IT CAN THEN BE INTERACTED WITH A LABELED PROBE. IF THE PROBE STICKS AND IT'S LABELED, THAT LABELED PROBE IF IT'S RADIOACTIVITY, FOR EXAMPLE, WILL BE STUCK TO THE MEMBRANE AND IT'S THIS, THAT STICKING TO THE MEMBRANE, THAT YOU'RE GOING TO BE DETECTING.

THIS IS SHOWING YOU THIS SUCKING OF THE DNA THROUGH THIS HOLE, THIS IS A NYLON MEMBRANE AND AS THE DNA WERE TO GO THROUGH IT GETS STUCK IN A STRIPE BETWEEN -- YOU SEE A DNA MOLECULE REPRESENTED. AND IT WILL BE DENATURED EITHER USUALLY BEFORE YOU WOULD STICK IT TO THE MEMBRANE.

NOW, IN THE LABORATORY WE VERY OFTEN DO THIS, YOU HAVE TO DO THE REACTION IN A CLOSED ENVIRONMENT, SO WE DO IT ACTUALLY IN A PLASTIC BAG CALLED A SEALING UNIT. AND YOU ACTUALLY INTRODUCE THE LIQUID INTO THE BAG WHERE THE MEMBRANE IS, AS YOU SEE HERE, AND THIS LIQUID THAT'S BEING INTRODUCED WILL HAVE THE LABELED PROBE ADDED.

AND YOU SEAL IT UP IN THIS SEALING DEVICE AND THEN YOU'LL PUT IT INTO A INCUBATOR SO YOU CAN INCUBATE IT FOR SOME TIME TO LET THE INTERACTION OCCUR.

WHAT HAPPENS DURING THAT TIME THIS LABELED PROBE THEN WILL FIND ITS COMPLIMENTARY SITE ON THE DNA AND STICK IF IT'S PRESENT. IF IT'S PRESENT IT WILL STICK AND YOU'LL SEE, YOU SEE IT HERE, BOUND OR ATTACHED TO THE TARGET DNA STRAND THAT'S STUCK

TO THE MEMBRANE.

AFTER YOU'VE DONE THAT YOU HAVE TO GET RID OF OR REMOVE THE PROBE THAT DIDN'T STICK BECAUSE THERE ISN'T DNA EVERYWHERE, ONLY IN THE SLOTS. SO YOU HAVE TO WASH IT AWAY AND THEN YOU PUT IT IN SOMETHING CALLED A CASSETTE AND EXPOSE TO X-RAY FILM. JUST LIKE AN X-RAY PROCESS WHERE X-RAYS EXPOSE FILM YOU GET A CHEST X-RAY OR SOMETHING THE RADIOACTIVITY IN THE PROBE WILL EXPOSE THE FILM, TOO.

YOU LEAVE IT FOR SOME TIME SO THE RADIOACTIVITY WILL EXPOSE THE FILM AND THEN THIS IS AN EXAMPLE OF A FILM WHERE THERE'S BEEN A NUMBER OF DNA SAMPLES PLACED IN THOSE SLOTS AND THEN THE ENTIRE FILTER HYBRIDIZED, THEN EXPOSED TO X-RAY FILM.

THIS IS THE X-RAY FILM, YOU GET BANDS ON THE X-RAY FILM, THE INTENSITY OR THE DARKNESS ACTUALLY AS IT TURNS OUT IS THE SIZE AS YOU EXPOSE IT MORE AND MORE IN SIZE, TOO, A LITTLE BIT, BUT ANYWAY THE AMOUNT OF BLACKNESS THAT IS PRODUCED IS AN INDICATION OF HOW MUCH PROBE HAS STUCK, WHICH IN TURN IS AN INDICATION OF HOW MUCH DNA MUST HAVE BEEN ON THE FILTER IN THE FIRST PLACE.

SOME TIMES THERE MAY BE NO SIGNAL, THAT WOULD SAY THERE WAS NO DNA AND SOMETIMES THERE MIGHT BE A LOT OF SIGNAL, THAT WOULD SAY THERE'S A LOT OF DNA. SO WHAT YOU JUST SAW IS STEPS D AND E OF THE -- OF CLAIM 1.

Q. THANK YOU, DOCTOR.

NOW, DOCTOR, WITH RESPECTS TO STEPS A THROUGH C, THE

AMPLIFICATION STEPS, DO YOU HAVE AN OPINION AS TO WHETHER OR NOT THOSE STEPS ARE TAUGHT BY EACH OF THE THREE KHORANA PRIOR ART REFERENCES WE'VE BEEN TALKING ABOUT, THE KLEPPE, NSF AND PANET?

A. YES, I THINK YOU CAN SEE AS I WENT THROUGH THE AMPLIFICATION PROCESS ON THE CHART IT'S EXACTLY THE SAME PROCESS WE'VE BEEN TALKING ALL ALONG. THE PROCESS OF SEQUENTIAL ROUNDS, TWO ROUNDS ACTUALLY OF PRIMER EXTENSION AND THAT'S WHAT WAS TAUGHT BY THE KHORANA REFERENCES.

Q. AND STEPS D AND E ARE THE PROBE HYBRIDIZATION OR PROBE DETECTION PROCEDURES THAT YOU DESCRIBE WITH THE HELP OF THE EXHIBITS, WERE THOSE PROCEDURES KNOWN TO THOSE OF ORDINARY SKILL IN THE ART IN EARLY 1984 AND BEFORE?

A. YES, HYBRIDIZATION IS A ROUTINE LABORATORY PROCEDURE. IT'S COMMON TO USE HYBRIDIZATION AS A WAY OF DETECTING PARTICULAR NUCLEIC ACID SEQUENCES. THAT'S BASICALLY WHAT MOLECULAR BIOLOGISTS ARE INTERESTED IN IS WHERE IS MY SEQUENCE OR HOW MUCH OF MY SEQUENCE DO I HAVE AND THE PROCESS YOU USE TO ASK THOSE QUESTIONS IS HYBRIDIZATION. IT'S QUITE ROUTINE AND IT WAS ROUTINE IN 1984.

Q. HAVE YOU CONDUCTED RESEARCH IN THAT AREA YOURSELF?

A. YES, THAT'S PROBABLY THE AREA I SPENT MOST OF MY CAREER EXPLOITING -- EXPLORING.

Q. AND YOU PUBLISHED PAPERS IN THAT FIELD?

A. YES, I HAVE.

Q. LET ME HAND YOU A COUPLE OF PAPERS, THEY'VE BEEN MARKED AS

EXHIBITS A-6 AND A-7 AND ASK YOU IF CAN IDENTIFY THEM FOR THE JURY?

A. YES, THESE ARE TWO PAPERS PUBLISHED BY MYSELF AND OTHERS, WHICH THEY WERE BOTH PUBLISHED IN 1981 AND THEY BOTH DESCRIBE THE USE OF HYBRIDIZATION PROBES, OLIGONUCLEOTIDE HYBRIDIZATION PROBES FOR DETECTION OF DNA SEQUENCES, SPECIFIC DNA SEQUENCES.

Q. DID THE PROCEDURES REFLECTED IN THESE PAPERS BECOME -- WERE THEY USED BY OTHER SCIENTISTS IN THE FIELD OF MOLECULAR BIOLOGY IN THE EARLY '80S?

A. THIS PROCEDURE THAT WE WERE DESCRIBING IN THESE PAPERS BECAME EXTREMELY IMPORTANT IN MOLECULAR BIOLOGY AND BIOTECHNOLOGY IN GENERAL BECAUSE IT GAVE THE SCIENTISTS IN THOSE FIELDS AN APPROACH TO IDENTIFY SPECIFIC DNA'S THAT WERE OF INTEREST OR EVEN OFTEN OF COMMERCIAL INTEREST.

SO YOU COULD USE THESE STRATEGIES TO IDENTIFY INTERESTING CLONE DNA'S, DNA'S WHICH HAD BEEN INTRODUCED INTO BACTERIA. FOR EXAMPLE, TISSUE PLEDGE ACTIVATOR WAS OBTAINED BY THIS STRATEGY AND ALLOWED THE WORKERS TO IDENTIFY THOSE CLONE DNA'S THE DNA'S THEY WANTED TO OBTAIN AND THEN USE THE CLONES ULTIMATELY TO PRODUCE, TO MANUFACTURER BIOLOGICALLY IMPORTANT MOLECULES IN BACTERIA.

Q. AS YOU'VE DESCRIBED CLAIM 1, IS IT CORRECT TO SAY IT COMBINES AN AMPLIFICATION STEP WITH A PROBE DETECTION STEP?

A. YES, I THINK THAT'S A FAIR STATEMENT.

Q. ARE YOU AWARE OF ANY OTHER PRIOR ART, PRIOR TO 1984 THAT

TEACHES DETECTING DNA USING A PROBE WHERE THE DNA HAS FIRST BEEN AMPLIFIED?

A. WELL, IN REALITY THAT'S WHAT THESE PAPERS, FOR EXAMPLE, DEMONSTRATE BECAUSE IN INTRODUCING A DNA INTO A BACTERIA AND THEN ALLOWING THAT BACTERIA TO REPLICATE THAT DNA IS A FORM OF AMPLIFICATION. AND ONCE IT'S AMPLIFIED WITHIN THE BACTERIA ITS HYBRIDIZATION IS USED TO DETECT THOSE SEQUENCES.

Q. LET ME SHOW YOU ANOTHER ARTICLE THAT WE HAVE MARKED AS EXHIBIT A-116.

CAN YOU IDENTIFY THAT ARTICLE?

A. THIS IS AN ARTICLE PUBLISHED IN 1979 BY GERGEN, STERN AND WENSINK AND, YES, I CAN IDENTIFY IT. IT'S A METHOD WHICH ACTUALLY MY LAB USED TO DO THE AMPLIFICATION STEPS.

THE WAY IT WORKS IS THAT YOU HAVE BACTERIA, WHICH HARBOR A PARTICULAR PIECE OF CLONE DNA, FOREIGN DNA HAS BEEN INTRODUCED INTO THESE BACTERIA PLASMA AND WHICH I EXPLAINED IS A CIRCULAR MOLECULE WHICH IS MAINTAINED IN THE BACTERIA.

IF YOU EXPOSE THOSE BACTERIA TO A PARTICULAR ANTIBIOTIC THE PLASMA IS COPYING THEM WITHIN THE BACTERIA THE NUMBER OF MASS INCREASES, IT'S INCREASED BY AMPLIFICATION STEP WHICH IS USED FOR SUBSEQUENT HYBRIDIZATION TO ALLOW YOU TO DETECT SPECIFIC SEQUENCES IN THE CLONES THAT YOU CREATED.

Q. WHY WERE SCIENTISTS INTERESTED IN AMPLIFYING AND THEN USING THE PROBE DETECTION PROCEDURE?

A. WELL, IT IMPROVES WHAT WE CALL THE SIGNAL TO NOISE. ANY OF

THESE HYBRIDIZATION STEPS HAVE PARTICULAR LEVEL OF KNOWN SPECIFICITY ATTACHED TO THEM AND IF YOU INCREASE THE NUMBER OF COPIES OF THE TARGET THEN YOUR CHANCES OF PICKING UP A BETTER SIGNAL AND WITH RESPECT TO THE NOISE ARE IMPROVED.

Q. HAVE YOU FORMED AN OPINION AS TO WHETHER OR NOT IT WOULD HAVE BEEN OBVIOUS TO A SCIENTISTS OF ORDINARY SKILL IN EARLY 1984 TO USE THESE PROBE DETECTION PROCEDURES ON DNA THAT HAD BEEN AMPLIFIED BY THE PROCEDURES DESCRIBED IN THE THREE KHORANA REFERENCES WE'VE BEEN TALKING ABOUT?

A. YES, I THINK THAT IT WOULD HAVE BEEN OBVIOUS. PARTICULARLY BECAUSE THIS IS SUCH A BROAD CLAIM. JUST SAYS BASICALLY AMPLIFY BY TWO ROUNDS OF PRIMER EXTENSION, WHICH KHORANA TAUGHT, AND THEN DETECT BY HYBRIDIZATION WHICH WAS RATHER ROUTINE IN THE LABORATORY. THERE'S NOT VERY MANY OTHER WAYS YOU COULD HAVE IMAGINED DOING THE DETECTION.

Q. LET'S NOW TURN TO SOME OF THE OTHER CLAIMS IN THE '195 PATENT, DR. WALLACE. CLAIM TWO READS THE PROCESS OF CLAIM 1, WHEREIN STEPS B AND C ARE REPEATED AT LEAST ONCE.

DO YOU HAVE AN OPINION AS TO WHETHER OR NOT THE SUBJECT MATTER CLAIMED IN THIS CLAIM WOULD HAVE BEEN OBVIOUS TO A SCIENTISTS OF ORDINARY SKILL IN EARLY 1984?

A. YES. WELL, THIS IS JUST THE REPEATING OF THE SECOND ROUND WHICH IS D AND C, AS THE SECOND ROUND TO PRODUCE A THIRD ROUND. SO AS WE TALKED ABOUT YOU CAN GO THROUGH THESE ROUNDS OF AMPLIFICATION TIME AND TIME AGAIN. SO THIS IS COVERED BY THE

KHORANA PRIOR ART.

Q. IS IT YOUR -- DO YOU HAVE AN OPINION WHETHER THE PROCESS CLAIMED IN THIS CLAIM WAS OBVIOUS OVER THE KHORANA PRIOR ART IN VIEW OF THE LITERATURE YOU'VE DISCUSSED ON PROBE HYBRIDIZATION?

A. YES. IT WAS OBVIOUS TO REPEAT THE AMPLIFICATION PROCESS AND YET ANOTHER TIME, THEN USE HYBRIDIZATION AS THE DETECTION SYSTEM.

Q. I'VE PLACED A BLOW UP OF CLAIM THREE ON THE EASEL IT READS: "THE PROCESS OF CLAIM 1, WHEREIN STEPS A AND C ARE ACCOMPLISHED BY TREATMENT WITH FOUR DIFFERENT NUCLEOSIDE TRIPHOSPHATES AND AN AGENT FOR POLYMERIZATION WHICH ARE ADDED TOGETHER WITH OR SEPARATELY FROM THE PRIMERS."

MAYBE FIRST IT WOULD BE USEFUL FOR YOU TO COME DOWN AND EXPLAIN WHAT SOME OF THESE TERMS MEAN AND THEN I'LL ASK YOU ABOUT THE RELATIONSHIP OF THE CLAIM TO THE PRIOR ART.

A. OKAY. THE FOUR DIFFERENT NUCLEOSIDE TRIPHOSPHATES FROM THE BUILDING BLOCKS THAT DR. KORNBERG TALKED ABOUT AND IT IS, THESE ARE THE BUILDING BLOCKS THAT THE POLYMERASE THAT, FOR EXAMPLE, DNA POLYMERASE USES TO DO THE PRIMER EXTENSION REACTION. THERE ARE FOUR OF THEM A, C, T AND G AND AN AGENT FOR POLYMERIZATION WOULD SIMPLY BE ANYTHING WHICH WOULD CAUSE THE PRIMER EXTENSION REACTION TO HAPPEN. DNA POLYMERASE IS THE MOST LIKELY AGENT FOR POLYMERIZATION, PERHAPS THE ONLY ONE.

THEN WHICH ARE ADDED TOGETHER WITH OR SEPARATELY FROM THE PRIMERS, SO THEY'RE JUST INDICATING THAT YOU COULD ADD THESE

MATERIALS BEFORE YOU BEGIN STEP A OR AFTER YOU -- YOU DON'T HAVE TO ADD THEM ALTOGETHER. I GUESS JUST SOME SORT OF LANGUAGE TO COVER ALL POSSIBILITIES.

AS I SAID CLAIM 1 IS QUITE BROAD. IT DOESN'T SPECIFICALLY SAY THAT YOU WOULD HAVE USED AN AGENT FOR POLYMERIZATION. SO THIS CLAIM JUST FURTHER NARROWS, I GUESS, THIS CLAIM, AND IT DOESN'T SAY THAT YOU WOULD HAVE ADDED THE FOUR DIFFERENT NUCLEOSIDE TRIPHOSPHATES. AGAIN, THAT'S JUST SPECIFYING A WAY OF DOING STEPS A AND C.

Q. DO YOU HAVE AN OPINION WHETHER OR NOT THE PROCESS DESCRIBED IN THIS CLAIM WAS OBVIOUS IN VIEW OF THE KHORANA PRIOR ART AND THE PROBE DETECTION TECHNOLOGY YOU'VE DESCRIBED?

A. YES, IT WOULD HAVE BEEN OBVIOUS. DR. KHORANA'S PRIOR ART TELLS YOU TO DO -- TO USE THE DNA POLYMERASE. THE DNA POLYMERASE WHICH IS AN AGENT FOR POLYMERIZATION REQUIRES THE FOUR DIFFERENT NUCLEOSIDE TRIPHOSPHATES AND SO IT WAS TAUGHT BY THE KHORANA PRIOR ART.

Q. OKAY. NOW, I'VE PLACED CLAIM FOUR ON THE EASEL IT READS: "THE PROCESS OF CLAIM 1, WHEREIN SAID NUCLEIC ACID IS DOUBLE STRANDED AND ITS STRANDS ARE SEPARATED BY DENATURING BEFORE OR DURING STEP A."

DO YOU HAVE AN OPINION WHETHER THIS ONE WAS OBVIOUS OVER THE KHORANA PRIOR ART AND THE PROBE DETECTION LITERATURE YOU DESCRIBED?

A. YES, THIS IS EXACTLY WHAT DR. KHORANA'S WORK SAID. YOU

START WITH A DOUBLE STRANDED DNA AND THE STRANDS ARE SEPARATED BY DENATURING, AS WE'VE GONE THROUGH THIS SO MANY TIMES NOW I THINK YOU CAN APPRECIATE THAT.

AGAIN, THIS IS A CLAIM WHICH FURTHER DEFINES HOW YOU DO CLAIM 1. SO YOU CAN SEE IN CLAIM 1 IT SAID A PROCESS FOR DETECTING THE PRESENCE OR ABSENCE OF AT LEAST ONE SPECIFIC NUCLEIC ACID SEQUENCE. WELL, THAT NUCLEIC ACID SEQUENCE COULD HAVE BEEN SINGLE STRANDED, DOUBLE STRANDED, SO THIS CLAIM SAYS IT'S DOUBLE STRANDED FURTHER LIMITING THIS CLAIM.

Q. OKAY. I PUT CLAIM SIX ON THE EASEL IT SAYS:

"THE PROCESS OF CLAIM 4, WHEREIN SAID NUCLEIC ACID IS DNA AND SAID PRIMERS ARE OLIGODEOXYRIBONUCLEOTIDES."

DO YOU HAVE AN OPINION WHETHER THIS CLAIM DESCRIBES A PROCESS THAT WAS OBVIOUS IN VIEW OF DR. KHORANA'S PRIOR ART?

A. WE JUST DISCUSSED CLAIM 4 WHICH SAID THAT IT COULD HAVE -- THAT THE NUCLEIC ACID IS DOUBLE STRANDED, BUT THERE ARE MORE THAN ONE KIND OF NUCLEIC ACID, THERE COULD BE DNA OR RNA.

SO THIS CLAIM NOW SAYS THAT IT'S DOUBLE -- THAT IT'S DNA AND CLAIM 4 SAID IT'S DOUBLE STRANDED, THAT MEANS IT'S DOUBLE STRANDED DNA AND THE PRIMERS ARE OLIGODEOXYRIBONUCLEOTIDES. SO REMEMBER WE DISCUSSED THIS BEFORE THIS OLIGO MEANS SHORT, SHORT NUCLEIC ACID SEQUENCE AND THE DEOXYRIBO MEANS IT'S DNA, SO THIS FURTHER DEFINES WHAT THE PRIMERS ARE, THE PRIMERS ARE SHORT PIECES OF DNA. AND THAT'S EXACTLY WHAT DR. KHORANA'S LAB WAS DOING, USING DOUBLE STRANDED

DNA AND DNA PRIMERS.

Q. I'VE PLACED CLAIM 11 ON THE EASEL, IT READS:

"THE PROCESS OF CLAIM 1, WHEREIN THE SPECIFIC NUCLEIC ACID SEQUENCE CONTAINS AT LEAST ONE SPECIFIC DELETION OR MUTATION THAT CAUSES A GENTIC DISEASE."

AGAIN, DO YOU HAVE AN OPINION AS TO WHETHER THE SUBJECT MATTER CLAIMED IN THIS CLAIM WAS OBVIOUS OVER THE KHORANA PRIOR ART IN VIEW OF THE PROBING LITERATURE?

A. FIRST -- YES, FIRST, I SHOULD EXPLAIN SOME OF THESE TERMS. FIRST OF ALL, WHAT IS A GENTIC DISEASE. A GENTIC DISEASE IS A DISEASE THAT YOU INHERIT FROM YOUR PARENTS THROUGH YOUR GENES AND A GENTIC DISEASE IS A CHANGE IN THE GENE.

THE GENES ARE MADE UP OF BUILDING BLOCKS, AS YOU'VE HEARD, SO IF THE BUILDING BLOCKS CHANGED THEN YOU CAN OFTEN BUT NOT ALWAYS, BUT OFTEN GET A GENTIC DISEASE. THE GENE BEGINS TO MALFUNCTION AND CREATES A PROBLEM WHICH MANIFESTS ITSELF AS A DISEASE.

THOSE CHANGES ARE CALLED, ARE OFTEN CALLED MUTATIONS CHANGES WHICH IS WHAT THE WORD MEANS AND THEY CAN BE CAUSED BY JUST A CHANGE AND A GOES TO A, T WOULD BE A CHANGE AND THAT COULD CAUSE A DISEASE, BUT ALSO COULD BE CAUSED BY REMOVING SEQUENCES -- BUILDING BLOCKS FROM THE GENE, SO IF YOU GOT SOME MISSING OR ACTUALLY EVEN IF YOU HAVE SOME INSERTED, THEN THAT CAN CAUSE THE GENE TO MALFUNCTION. THIS CLAIM TALKS ABOUT DELETION THAT'S REMOVING THOSE SEQUENCES.

IN 1984 IT WAS WELL-KNOWN THAT YOU COULD USE OLIGODEOXYRIBONUCLEOTIDES PROBES TO DETECT THOSE DIFFERENCES YOU COULD TELL THE DIFFERENCE BETWEEN A NORMAL GENE AND A CHANGED GENE BY THE FACT THAT PERHAPS WE COULD SHOW ON THIS CHART HERE.

Q. UH-HUH.

A. BY THE FACT THAT THE PROBE WOULD INTERACT WITH THE GENE IF IT HAD THE CORRECT SEQUENCE, BUT IF IT HAD THE INCORRECT SEQUENCE IT COULDN'T INTERACT EVEN IF -- EVEN IF THERE WAS ONLY ONE CHANGE, ONE DIFFERENCE BETWEEN PROBE AND THE TEMPLATE, I CAN'T REALLY SHOW YOU THAT BECAUSE THERE'S MANY CHANGES HERE, BUT THAT'S THE IDEA.

ACTUALLY MUCH OF THAT WORK WAS DONE IN MY OWN LABORATORY FOR A GENTIC DISEASE CALLED SICKLE CELL ANEMIA WHICH IS CAUSED BY A CHANGE IN ONE PARTICULAR A BEING CHANGED TO A T AND IF YOU INHERIT TWO COPIES, ONE FROM YOUR MOTHER AND ONE FROM YOUR FATHER, IT CREATES A GENTIC DISEASE CALLED SICKLE CELL ANEMIA AND YOU COULD DETECT THOSE CHANGES BY HYBRIDIZING WITH OLIGODEOXYRIBONUCLEOTID PROBES.

Q. IS THAT WORK PUBLISHED?

A. YES.

Q. LET ME HAND YOU A COPY OF AN EXHIBIT THAT'S BEEN MARKED AS B-146 AND ASK YOU IF YOU CAN IDENTIFY THAT?

A. YES, THIS IS A PAPER FROM MY LABORATORY BY CONNER AND OTHERS WHICH IS ENTITLED DETECTION OF CYCLE CELL BETA GLOBIN ANEMIA BY HYBRIDIZATION BY SYNTHETIC OLIGONUCLEOTIDES.

FIRST AN ANNEAL IS ONE COPY, FOR EXAMPLE, THE COPY INHERITED FROM YOUR MOTHER IS ONE ANNEAL, THE COPY INHERITED FROM YOUR FATHER IS THE OTHER ANNEAL WE SHOWED YOU COULD DETECT THE PRESENCE OF ONE OR TWO BETA GLOBIN ANNEALS, THE BETA IS THE SICKLE CELL GLOBIN BECAUSE IT AFFECTS THE PROTEIN THAT'S IN YOUR BLOOD THAT MAKES YOUR BLOOD RED CALLED HEMAGLOBIN AND THE GENE THAT MAKES ONE OF THOSE PROTEINS IS CALLED BETAGLOBIN, SO THIS PAPER DESCRIBED HOW YOU COULD DETECT SICKLE CELL GLOBIN IN HUMAN DNA.

Q. USING A PROBE?

A. USING SYNTHETIC OLIGODEOXYRIBONUCLEOTIDE PROBES.

Q. WHEN WAS THAT ARTICLE PUBLISH, DR. WALLACE?

A. JANUARY OF '83.

Q. LET ME SHOW YOU ANOTHER ARTICLE OR PATENT ACTUALLY THAT WE HAVE MARKED AS EXHIBIT A-102.

FIRST OF ALL, COULD YOU IDENTIFY THAT FOR THE JURY?

A. THIS IS A PATENT CALLED PROCESS FOR LABELING NUCLEIC ACID. NUCLEIC ACIDS USING PSORALEN DERIVATIVES, SHELDON, LEVENSON, MULLIS, AND RAPOPORT OF THE CETUS CORPORATION ARE THE INVENTORS.

Q. WHEN WAS THE APPLICATION FOR THAT PATENT INITIALLY FILED?

A. DECEMBER OF '84. THIS IS BASICALLY A PATENT FOR DESCRIBING HOW YOU LABEL. I TOLD YOU YOU COULD LABEL IT WITH RADIOACTIVITY, BUT THERE ARE MANY OTHER WAYS YOU CAN LABEL, AS LONG AS YOU HAVE A WAY OF DETECTING IT AND THIS PATENT DESCRIBES ANOTHER WAY OF LABELING IT.

Q. DOES THE CETUS PATENT CONTAIN ANY DISCUSSION OF THE STATE OF THE ART AS OF THE TIME IT WAS FILED?

A. WELL IN THE BACKGROUND SECTION IT BASICALLY DESCRIBES THE FACT THAT HYBRIDIZATION WAS A KNOWN METHOD FOR DETECTING PARTICULAR NUCLEIC ACID SEQUENCES AND MUTATIONS. FOR EXAMPLE, IT SAYS . . . I'M TRYING TO FIND THE SECTION HERE.

"SUCH PROBES HAVE BEEN USED TO DETECT THE PRESENCE OF GENES CODING FOR ANTIGENS RESPONSIBLE FOR GRAFT REJECTION , SUCH AS HUMAN LEUKOCYTE ANTIGEN OR GENETIC DISEASE, SUCH AS SICKLE CELL ANEMIA."

Q. THAT'S DESCRIBED AS PART OF THE BACKGROUND FOR THE PRIOR ART?

A. YES.

Q. DOCTOR, CAN YOU SUMMARIZE YOUR OPINION THEN AS TO WHETHER OR NOT THE SUBJECT MATTER OF CLAIM 11 WAS -- WOULD HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN 1984 IN VIEW OF THIS LITERATURE YOU HAVE DISCUSSED?

A. YES. THE WAY I VIEW IT MUTATED OR CHANGED NUCLEIC ACID SEQUENCES ARE DIFFERENT NUCLEIC ACID SEQUENCES AND THEY CAN BE DETECTED BY HYBRIDIZATION AND THE HYBRIDIZATION WAS A WELL-KNOWN PROCESS, SO IT WOULD HAVE BEEN OBVIOUS TO AMPLIFY THEN DETECT.

Q. DOCTOR, DO YOU SEE ANY OF THIS CLAIM THAT TELLS WHETHER THE SEQUENCE BEING AMPLIFIED IS IN A COMPLEX MIXTURE OF DNA OR CAN IT BE ISOLATED AS A SMALL SEGMENT OF DNA FOR AMPLIFICATION?

A. SINCE IT REFERS BACK TO CLAIM 1 CAN BE A DNA THAT'S PRESENT

OR ABSENT IN AT LEAST ONE SPECIFIC NUCLEIC ACID SEQUENCE. IT DOESN'T HAVE TO BE A COMPLEX MIXTURE, BE A SIMPLE NUCLEIC ACID SEQUENCE THAT HAD BEEN PREVIOUSLY ISOLATED, FOR EXAMPLE.

Q. AND DO SCIENTISTS, PRIOR TO 1984, DO SCIENTISTS SOMETIMES ISOLATE DNA THEN USE THE HYBRIDIZATION TECHNIQUE?

A. YES. YES, THEY WOULD ISOLATE BY CLONING AS I DESCRIBED, BY INTRODUCING THE SEQUENCES INTO BACTERIA, THEN YOU COULD USE THE HYBRIDIZATION TECHNIQUES TO ANALYZE THOSE PIECES OF DNA.

Q. THANK YOU, DOCTOR. THE NEXT ONE IS CLAIM 12. CLAIM 12 WHICH I'VE PLACED ON THE EASEL READS:

"THE PROCESS OF CLAIM 11, WHEREIN THE GENTIC DISEASE IS SICKLE CELL ANEMIA."

DO YOU HAVE AN OPINION ABOUT WHETHER THIS IS OBVIOUS IN VIEW OF THE PRIOR ART YOU'VE BEEN DISCUSSING?

A. AS I SAID, WORK FOR MY OWN LABORATORY SHOWED YOU COULD DETECT SICKLE CELL BY HYBRIDIZATION AND THAT JUST FURTHER DEFINES CLAIM 11 WHICH I'VE ALREADY SAID WAS OBVIOUS.

MR. PASAHOW: EXCUSE ME, YOUR HONOR. CLAIM 12 IS NOT AT ISSUE IN THIS CASE AS THE ISSUES WERE DEFINED BY THE PARTIES PRETRIAL STATEMENTS AND THE COURT'S ORDER. I OBJECT TO TESTIMONY ABOUT IT.

THE COURT: FOR WHAT PURPOSE?

MR. FIGG: WE'LL MOVE ON TO THE NEXT SUBJECT.

THE COURT: IS THAT ACKNOWLEDGEMENT THAT I SHOULD STRIKE THE PRECEDING ANSWER?

MR. FIGG: MAY WE TAKE THAT UNDER IS ADVISEMENT, YOUR HONOR AND DISCUSS IT AFTER A BREAK BECAUSE WE CAN LOOK UP THAT SUBJECT, THAT QUESTION. NOW, MR. PASAHOW MAY BE RIGHT I MIGHT HAVE JUST PLACED A CHECK MARK BY THE WRONG CLAIM.

THE COURT: I THINK HE IS RIGHT. THAT DOESN'T NECESSARILY MEAN ONE CAN'T GO INTO OTHER CLAIMS, BUT IT HAS TO THEN SHED LIGHT UPON THOSE THAT ARE IN ISSUE AND NOT RAISE THE ISSUES OF THE CLAIMS THEMSELVES.

MR. FIGG: JUST A MOMENT.

THE COURT: AND I THINK YOUR LAST QUESTION DID THAT.

MR. FIGG: I'M SORRY.

THE COURT: AND I THINK YOUR LAST QUESTION DID, IN FACT, APPEAR TO PUT 12 IN ISSUE AS WELL.

(PAUSE IN THE PROCEEDINGS)

THE COURT: ARE YOU REFERRING TO THIS AS SOMETHING THAT'S IN YOUR PRETRIAL ORDERS OR COMPLAINT OR SOMETHING THAT WAS TAKEN UP AT THE PRETRIAL ITSELF?

MR. PASAHOW: YOUR HONOR, IN THE PARTIES JOINT PRETRIAL CONFERENCE STATEMENT --

MR. FIGG: EXCUSE ME, IF I COULD INTERRUPT. MR. PASAHOW IS CORRECT WE'LL WITHDRAW THOSE QUESTIONS.

THE COURT: THE JURY IS INSTRUCTED TO DISREGARD ALL THE QUESTIONS AND ANSWERS WITH RESPECT, AND I THINK THERE WERE ONLY TWO OF THEM, WITH RESPECT TO CLAIM 12.

Q. (BY MR. FIGG) DR. WALLACE, I'VE PLACED ON THE EASEL NOW

CLAIM 14 IT READS:

"THE PROCESS OF CLAIM 1, WHEREIN THE SPECIFIC NUCLEIC ACID SEQUENCE IS CONTAINED IN A PATHOGENIC ORGANISM OR CONTAINED IN THE ONCOGENE."

DO YOU HAVE AN OPINION AS TO WHETHER THE SUBJECT MATTER CLAIMED IN THIS CLAIM IS OBVIOUS IN VIEW OF THE KHORANA PRIOR ART AND THE LITERATURE YOU'VE BEEN DISCUSSING?

A. YES, BUT FIRST LET ME EXPLAIN A PATHOGENIC ORGANISM. ORGANISMS I THINK YOU UNDERSTAND WHAT AN ORGANISM IS. ALL ORGANISMS CONTAIN NUCLEIC ACIDS, SO BACTERIA, FISH AND US ARE ALL ORGANISMS AND THEY ALL CONTAIN NUCLEIC ACIDS AND THOSE NUCLEIC ACIDS ARE SUFFICIENTLY DIFFERENT BETWEEN ORGANISMS THAT YOU CAN TELL DIFFERENCE BETWEEN DIFFERENT ORGANISMS BY THEIR NUCLEIC ACID.

AND ONE WAY TO DO THAT IS THROUGH HYBRIDIZATION, SO BECAUSE THE PROBE CAN BE SPECIFIC FOR A PARTICULAR ORGANISM YOU CAN SAY THIS ORGANISM IS X AND NOT Y BECAUSE YOU KNOW THAT THE PROBE WOULD INTERACT WITH THE NUCLEIC ACID OF X AND NOT THE NUCLEIC ACID OF Y, SO THAT'S WHAT A PATHOGENIC ORGANISM IS.

AN ONCOGENE IS A GENE WITHIN OUR BODIES THAT WE'VE INHERITED OR ACQUIRED WHICH CAUSES ONCOGENESIS OR CANCER OR SO AN ONCOGENE IS A GENE THAT WOULD HAVE A PARTICULAR NUCLEIC SEQUENCE OF NUCLEOTIDES WITHIN THE GENE.

AND AGAIN BECAUSE HYBRIDIZATION CAN BE USED TO DISCRIMINATE BETWEEN ONE GENE AND ANOTHER GENE YOU COULD USE

HYBRIDIZATION TO ANALYZE FOR ONCOGENE AND THEREFORE POTENTIALITY CREATE A TEST FOR CANCER LET'S JUST SAY FOR EXAMPLE.

BUT THE BASIC PRINCIPLE IS NUCLEIC, THAT EACH NUCLEIC ACID CAN BE DETECTED BY HYBRIDIZATION WITH A PROBE, SO THIS PROCESS JUST SIMPLY DEFINES A COUPLE OF DIFFERENT KINDS OF NUCLEIC ACID SEQUENCES, BUT IN FACT ANY DIFFERENT NUCLEIC ACID SEQUENCE COULD BE DETECTED BY HYBRIDIZATION. SO THIS JUST IS REFINING THE NUCLEIC ACID SEQUENCES THEY'RE TALKING ABOUT IN CLAIM 1 SO IT'S OBVIOUS.

Q. LET ME SHOW YOU A DOCUMENT THAT'S BEEN MARKED AS EXHIBIT A-20. CAN YOU IDENTIFY THAT DOCUMENT?

A. THIS IS ANOTHER PATENT THAT CALLED SPECIFIC DNA PROBES AND DIAGNOSTIC MICROBIOLOGY BY FALKOW AND OTHERS AND IT WAS FILED IN 1980 AND BASICALLY WHAT THIS PATENT SAYS IS THAT YOU CAN USE THE SPECIFICITY WITH WHICH A DNA PROBE CAN DETECT AN ORGANISM'S ACIDS AND SAY FOR THAT ORGANISM AND IT'S BASICALLY DESCRIBING A WAY OF DOING TEST FOR PATHOGENIC ORGANISMS USING HYBRIDIZATION PROBES.

Q. YOU PREVIOUSLY DISCUSSED THE SHELDON PATENT THAT'S ASSIGNED TO CETUS DOES THAT DISCUSS USING PROBES FOR DETECTING PATHOGENIC ORGANISMS AS PART OF THE STATE OF THE PRIOR ART?

A. YES, AGAIN, IN THE BACKGROUND SECTION IT DESCRIBES THAT: IN ADDITION U.S. PATENT NUMBER, PATENT I JUST DESCRIBED BY FALKOW AND OTHERS, DESCRIBE A METHOD FOR DETECTING INFECTIOUS DISEASE-CAUSING MICROBES USING LABELED NUCLEOTIDE PROBES, ARE

ONE CLASS OF PATHOGENIC ORGANISMS, USING LABELED NUCLEOTIDE PROBES COMPLIMENTARY TO NUCLEIC ACID CONTAINED BY PATHOGENIC MICROBE." SO THIS WAS WELL-KNOWN.

Q. DOCTOR, DO YOU SEE ANYTHING IN THE PROCESS DESCRIBED BY CLAIM 14 THAT INDICATES WHETHER THE DNA BEING DETECTED IS PART OF A COMPLEX MIXTURE OR A SPECIFIC SEQUENCE?

A. NO, AGAIN, SINCE THIS CLAIM REFERS BACK TO CLAIM 1, THE SPECIFIC NUCLEIC ACID SEQUENCE IN CLAIM 1, THIS SPECIFIC NUCLEIC ACID SEQUENCE COULD BE A SMALL PIECE OF NUCLEIC ACID INFORMATION WHICH WAS PREVIOUSLY ISOLATED, FOR EXAMPLE.

Q. I'VE PLACED ON THE EASEL A COPY OF CLAIM 15. "THE PROCESS OF CLAIM 1, WHEREIN STEPS A AND C ARE ACCOMPLISHED USING AN ENZYME SELECTED FROM THE GROUP CONSISTING OF E COLI POLYMERASE 1 KLENOW FRAGMENT OF E COLI POLYMERASE 1. THE FOUR DNA POLYMERASE REVERSE TRANSCRIPTASE WHEREIN THE TEMPLATE IS RNA OR DNA AND THE EXTENSION PRODUCT IS DNA AND AN ENZYME THAT AFTER BEING EXPOSED TO A TEMPERATURE ABOUT 65 TO 90 DEGREES CENTIGRADE FORMS SAID EXTENSION PRODUCTS AT THE TEMPERATURE OF ERECTION DURING STEPS A AND C."

DO YOU HAVE AN OPINION AS TO WHETHER THE PROCESS DESCRIBED BY THIS CLAIM WOULD HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN 1984?

A. WELL, YES, I DO HAVE AN OPINION. THIS CLAIM GOES BACK TO CLAIM 1, AND IT'S TALKING ABOUT STEPS A AND C WHICH ARE THE TWO PRIMER EXTENSION STEPS AND IT IS SAYING PRIMER EXTENSION STEPS

ARE ACCOMPLISHED BY AN ENZYME, A POLYMERASE AND IT GIVES YOU A LIST OF KINDS OF POLYMERASES. YOU'VE ALREADY HEARD THAT THE E COLI DNA POLYMERASE 1 WHICH IS THE ENZYME THAT WAS DISCOVERED BY DR. KORNBERG WAS BEING USED BY THE KHORANA LAB AS WAS THE FOUR DNA POLYMERASE.

THERE ARE OTHER ENZYMES, FOR EXAMPLE, REVERSE TRANSCRIPTASE IS AN ENZYME WHICH CAN USE RNA AS A TEMPLATE TO PRODUCE A DNA. SO IT SAYS WHEREIN THE TEMPLATE IS RNA OR DNA REVERSE TRANSCRIPTASE CAN ALSO USE DNA AS A TEMPLATE AND THE EXTENSION PRODUCT IS DNA JUST FINDING WHAT THE REVERSE TRANSCRIPTASE CAN DO, THEN AN ENZYME AFTER BEING EXPOSED TO A TEMPERATURE OF ABOUT 65 TO 90 DEGREES FORMED SAID EXTENSION PRODUCTS AT THE TEMPERATURE REACTION DURING STEPS A AND C.

THE EXTENSION STEPS SIMPLY IS DEFINING AN ENZYME THAT WE CALL THERMOSTABLE AN ENZYME THAT WILL SURVIVE BEING HEATED AND SUCH ENZYMES WERE KNOWN. SO THOSE ARE JUST A LIST OF THE POLYMERASE AT LEAST TWO OF WHICH WERE USED IN THE KHORANA WORK.

Q. THOSE WERE THE FIRST TWO WERE USED BY DR. KHORANA?

A. NO. THE E COLI DNA POLYMERASE 1, THE FIRST ONE AND THE THIRD ONE, THE FOUR DNA POLYMERASE.

Q. THANK YOU, DR. WALLACE.

DR. WALLACE, HAVE YOU REVIEWED ANY OF THE DOCUMENTS CONNECTED WITH THE RE-EXAMINATION OF THE '195 PATENT IN THE PATENT AND TRADEMARK OFFICE?

A. WELL, YES, I REVIEWED THE ONE DOCUMENT.

Q. LET ME SHOW YOU A DOCUMENT THAT HAS BEEN MARKED AS EXHIBIT A-88 AND ASK IF YOU CAN IDENTIFY THIS AS THE EXAMINER'S INITIAL ORDER ON ESTABLISHING A RE-EXAMINATION ON THE '195 PATENT?

A. YES, THIS IS WHAT I'VE LOOKED AT. IT WAS AN ORDER FROM THE EXAMINER THAT SAID THE REQUEST FOR RE-EXAMINATION IS GRANTED, BUT IT ONLY FOUND A SUBSTANTIAL NEW QUESTION OF PATENTABILITY AFFECTING CLAIMS 19 THROUGH 25, WHICH I BELIEVE WE'RE NOT EVEN DISCUSSING HERE AND SO THEREFORE FOUND NO QUESTION OF PATENTABILITY ON CLAIMS ONE THROUGH 18, I GUESS IT WOULD BE.

Q. NOW, YOU'VE REVIEWED THE PRIOR ART VERY CAREFULLY, DO YOU HAVE AN OPINION AS TO WHETHER OR NOT THE EXAMINER WAS CORRECT IN HIS DECISION ON THE RE-EXAMINATION OF THIS PATENT?

A. WELL, I DON'T UNDERSTAND WHY THE EXAMINER WOULD HAVE NOT FOUND A QUESTION OF PATENTABILITY IN CONSIDERING THE KHORANA PRIOR ART.

PARTICULARLY SINCE HE DID IN THE '202 PATENT WHICH IS THE SAME AMPLIFICATION PROCESS, SO THERE'S CERTAINLY AN ISSUE WITH RESPECT TO THAT. SO THE KHORANA PRIOR ART TEACHES THE AMPLIFICATION PROCESS AND I DON'T THINK HE WAS CORRECT IN MAKING HIS DECISION.

MR. FIGG: THANK YOU, DR. WALLACE. THAT CONCLUDES OUR DIRECT EXAMINATION, YOUR HONOR.

THE COURT: THANK YOU.

MR. FIGG: I JUST HAVE A FEW EXHIBITS TO MOVE IN, YOUR HONOR. WE MOVE THE ADMISSION OF EXHIBITS A-109 AND A-110.

A-109 A IS TWO PART POSTER BLOW UP OF PARTS OF THE HONG ARTICLE AND A-110 A IS A BLOW UP OF THE OTHER HONG ARTICLE.

THE COURT: ANY OBJECTIONS TO THOSE?

MR. PASAHOW: NO, YOUR HONOR.

THE COURT: THEY'RE ADMITTED.

(PLAINTIFF'S EXHIBITS A-109, A-110 RECEIVED IN EVIDENCE)

MR. FIGG: AND EXHIBITS A-47 AND A-108 ARE POSTER BLOW UPS OF EXCERPTS FROM DR. WALLACE'S ARTICLES.

MR. PASAHOW: NO OBJECTION.

THE COURT: ADMITTED.

(PLAINTIFF'S EXHIBITS A-47, A-108 RECEIVED IN EVIDENCE)

MR. FIGG: AND A-137 IS SIMPLY A BLOW UP OF CLAIM 1 OF THE '195 PATENT.

THE COURT: I ASSUME THERE'S NO OBJECTION.

MR. PASAHOW: NO OBJECTION.

THE COURT: ADMITTED.

(PLAINTIFF'S EXHIBIT A-137 RECEIVED IN EVIDENCE)

MR. FIGG: THANK YOU.

THE COURT: I THINK THE REPORTER TALKED WITH YOU ABOUT HOW THEY WANT TO BREAK UP THE MORNING, SO THAT THEY COULD GET THE TRANSCRIPT OUT. SO I GUESS THIS IS PROBABLY A GOOD TIME TO BREAK AND THEN WE'LL HAVE A LONG SECOND SEGMENT AND THEN OUR

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SECOND BREAK.

MR. FIGG: YES.

MR. PASAHOW: VERY GOOD.

THE COURT: TEN, 15 MINUTES. PLEASE FOLLOW THE INSTRUCTIONS I'VE GIVEN YOU'VE PREVIOUSLY ABOUT NOT DISCUSSING THE CASE AMONGST YOURSELVES OR WITH ANYONE ELSE AND WE'LL SEE YOU AT THE CLOSE OF THE RECESS.

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

THE COURT: WITH WHOM WILL YOU BE CALLING AFTER DR. WALLACE?

MR. FIGG: DOCTOR RUTH KLEPPE.

THE COURT: WILL WE GET TO HER THIS MORNING?

MR. FIGG: DEPENDS ON MR. PASAHOW.

THE COURT: I TRUST WE CAN. HOW LONG WILL YOU BE WITH HER ON DIRECT?

MR. FIGG: I THINK LESS THAN AN HOUR.

THE COURT: OKAY.

MR. PASAHOW: YOUR HONOR, AS TO DOCTOR KLEPPE, I THINK MR. FIGG AND I HAVE WORKED OUT A WAY OF CONTINUING TO POSTPONE, PROBABLY UNTIL THE RIGHT MOMENT, THE QUESTION OF WHETHER THE NOTEBOOKS THAT SHE WILL BE IDENTIFYING SHOULD BE ADMITTED INTO EVIDENCE.

MR. FIGG HAS EXPLAINED THAT HE DOESN'T PLAN TO SHOW THE CONTENTS TO THE JURY UNTIL WE GET TO THE TESTIMONY OF MR. VAN DE SANDE, AND AT THAT POINT HE WILL OR WILL NOT HAVE LAID WHAT WE

THINK IS THE NECESSARY FOUNDATION.

SO WE WOULD ASK THAT HE BE ALLOWED TO OFFER THEM DURING DOCTOR KLEPPE'S TESTIMONY AND WE WILL THEN HEAR WHAT THE OTHER WITNESSES HAVE TO SAY AND WE'D ASK THE COURT TO DELAY ITS RULING ON THAT QUESTION UNTIL WE GET TO DOCTOR VAN DE SANDE'S TESTIMONY.

THE COURT: IS THAT GOING TO NECESSITATE RECALLING DOCTOR KLEPPE THEN?

MR. FIGG: ACTUALLY, YOUR HONOR, MY UNDERSTANDING WAS SLIGHTLY DIFFERENT THAN MR. PASAHOW. WE THINK THAT PROPER FOUNDATION WILL BE LAID WITH DOCTOR KLEPPE. SHE WILL IDENTIFY NOTEBOOKS AS NOTEBOOKS THAT HER HUSBAND KEPT AND EXPLAIN WHAT THEY ARE AND WE'LL ESTABLISH A PROPER FOUNDATION FOR THEM. AND WE DID PLAN TO OFFER THEM INTO EVIDENCE AT THE CONCLUSION OF DOCTOR KLEPPE'S TESTIMONY.

DOCTOR VAN DE SANDE THEN WILL, AS AN EXPERT WITNESS, WILL EXPLAIN THE CONTENTS OF THOSE NOTEBOOKS AND EXPLAIN THEIR RELEVANCE TO THE SUBJECT MATTER OF THE PATENTS IN SUIT.

MR. PASAHOW IS CORRECT, WE DO NOT INTEND TO SHOW THE CONTENTS OF DOCTOR KLEPPE'S LATE HUSBAND'S NOTEBOOKS TO THE JURY DURING HER TESTIMONY. SHE WILL NOT BE SUBSTANTIVELY DESCRIBING WHAT IS IN THE NOTEBOOKS, BUT WILL ONLY BE DESCRIBING WHAT THE NOTEBOOKS ARE, WHAT THE EXHIBITS ARE AND SO FORTH.

THE COURT: AS A FOUNDATION THAT'S GOING TO GET LAID, IT'S GOING TO GET LAID THROUGH HER TESTIMONY.

MR. FIGG: THAT'S MY UNDERSTANDING.

THE COURT: NO ONE ELSE IS GOING TO BE ABLE TO FILL IN ANY GAPS WITH RESPECT TO THE FOUNDATION.

MR. FIGG: SHE'S THE ONE WHO WILL IDENTIFY THE NOTEBOOKS AND EXPLAIN HOW THEY WERE KEPT AND SO FORTH.

THE COURT: THAT'S YOUR UNDERSTANDING ALSO, RIGHT?

MR. PASAHOW: IT IS, YOUR HONOR. THIS IS THE SUBJECT MATTER OF THOSE VARIOUS MEMOS WE'VE BEEN FILING.

AS THE COURT KNOWS IT'S OUR POSITION THE NOTEBOOKS ARE NOT RELEVANT AND SHOULD NOT BE RECEIVED UNLESS MR. FIGG CAN LAY THE FOUNDATION THEY'RE APPROPRIATE PRIOR ART UNDER EITHER ONE, IN THAT THEY WERE PUBLICLY KNOWN OR ALTERNATIVELY THAT THEY WERE THE SUBJECT MATTER OF THEM WAS NOT SUPPRESSED OR CONCEALED UNDER 102(G) AND WE DON'T THINK HE CAN.

THE COURT: WELL, I GUESS THAT REMAINS TO BE SEEN.

MR. FIGG: THAT'S REALLY THE ISSUE TO BE DECIDE. WE'RE GOING TO EXPLAIN WHAT THEY ARE. THE JURY HAS TO DECIDE WHETHER THEY'RE --

THE COURT: IF HER TESTIMONY IS GOING TO CONTINUE INTO TOMORROW, HOPEFULLY GET STARTED TODAY BUT CONTINUE INTO TOMORROW, AND THEY'LL CERTAINLY BE SOME TIME TOMORROW AT THE CLOSE OF HER TESTIMONY TO GET THAT RESOLVED IT SEEMS.

IF THERE ARE STILL SOME QUESTIONS BECAUSE OF RELEVANCY TO HAVE TO WAIT DOCTOR VAN DE SANDE'S TESTIMONY THEN THAT WILL JUST HAVE TO WAIT, BUT AT LEAST ANY QUESTIONS I ASSUME ABOUT

BOTH CONCEALMENT OR WHATEVER AND AUTHENTICITY AND SO FORTH WILL HAVE BEEN AND WHEN THEY WERE PREPARED, ET CETERA, WILL OBVIOUSLY HAVE BEEN LAID THROUGH HER.

SO I GUESS ONLY POSSIBLY THEN THE RELEVANCY QUESTION MIGHT COME UP AFTER HER TESTIMONY.

MR. FIGG: THERE IS ONE NOTEBOOK THAT WE WILL -- AND I'VE EXPLAINED THIS TO MR. PASAHOW, WILL BE DESCRIBED TO THE JURY DURING DOCTOR KLEPPE'S TESTIMONY AND THAT IS HER OWN NOTEBOOK, A NOTE SHE KEPT OF A SEMINAR PRESENTATION BY HER LATE HUSBAND.

THE COURT: OKAY. AND YOU'RE AWARE OF ALL OF THAT ANYWAY?

MR. PASAHOW: YES, YOUR HONOR.

THE COURT: FINE. WHAT IS YOUR APPROXIMATION AS TO THE LENGTH OF CROSS?

MR. PASAHOW: WELL, IT MAY OR MAY NOT TAKE THE REST OF THE MORNING, YOUR HONOR, DEPENDING UPON HOW QUICKLY WE MOVE ALONG.

THE COURT: THAT'S USUALLY THE CASE. YOU'RE ANTICIPATING A LOT OF OBJECTIONS BY MR. FIGG.

MR. PASAHOW: NO, YOUR HONOR. IT DEPENDS UPON HOW RESPONSIVE THE WITNESS AND I ARE TO EACH OTHER.

THE COURT: I SEE. OKAY. WELL, HE CERTAINLY SPEAKS QUICKLY ENOUGH.

IS IT A PROBLEM FOR YOU, MR. YEOMANS?

I KNOW I DO THE SAME THING. IT'S USUALLY NOT WITH SUCH LARGE WORDS, SO THAT'S THE REAL TRICK.

OKAY. WE'LL SEE YOU IN ABOUT TEN MINUTES, TEN, 15.

(RECESS TAKEN)

(CONTINUED ON NEXT PAGE - NOTHING OMITTED)

(OPEN COURT, JURY PRESENT, AT 9:54 A.M.:)

MR. PASAHOW: SHALL I PROCEED, YOUR HONOR?

THE COURT: YOU MAY PROCEED, YES.

CROSS-EXAMINATION

BY MR. PASAHOW:

Q. GOOD MORNING, DR. WALLACE.

A. GOOD MORNING, MR. PASAHOW.

Q. DR. WALLACE, AT THE END OF YOUR DIRECT EXAMINATION, YOU WERE EXPLAINING SOME CONFUSION ABOUT HOW THE EXAMINER COULD HAVE COME TO THE DECISION HE DID IN THE INITIAL PARTS OF THE RE-EXAMINATION OF THE '195 PATENT.

A. YES, I WAS.

Q. NOW, YOU UNDERSTOOD THAT THE STANDARD THE EXAMINER WAS USING WAS WHETHER ANY REASONABLE PATENT EXAMINER COULD HAVE FOUND THAT THE MATERIAL THAT DU PONT SUBMITTED WOULD HAVE BEEN MATERIAL TO DECIDING WHETHER THE PATENT CLAIM SHOULD ISSUE.

MR. FIGG: OBJECTION, YOUR HONOR. THERE'S NO EVIDENCE THAT THAT'S THE STANDARD THE EXAMINER WAS FOLLOWING.

MR. PASAHOW: WELL --

THE COURT: IS THERE A DISPUTE ABOUT THAT?

MR. FIGG: WELL, YOUR HONOR, I THINK MR. PASAHOW IS EMBELLISHING ON THE STANDARD SOMEWHAT.

THE COURT: I THINK THE BETTER WAY TO DO IT IS TO ASK HIM IF HE -- IF HE UNDERSTANDS WHAT THE STANDARD IS AND, IF SO, TO ELICIT THAT FROM HIM. OTHERWISE, I MAY STRIKE THAT

TESTIMONY.

MR. PASAHOW: WELL, YOUR HONOR, THE STANDARD I JUST RECITED IS FROM THE MANUAL OF PATENT EXAMINING PROCEDURES. IT -- IT IS THE LEGAL STANDARD AND --

THE COURT: WELL, BUT THE PROBLEM IS THAT EITHER YOU'RE GOING TO HAVE TO HAVE A STIPULATION TO IT OR ASK THE COURT TO TAKE JUDICIAL NOTICE OF IT.

(PAUSE IN PROCEEDINGS)

THE COURT: I'LL ALLOW YOU TO ASK THE QUESTION, BUT I'M INSTRUCTING THE JURY THAT -- NOT TO ASSUME ANYTHING FROM THE ANSWER -- FROM THE QUESTION UNLESS THE ANSWER, IN FACT, IS IN THE AFFIRMATIVE. IF IT'S NOT, THEN YOU'LL HAVE TO AWAIT FURTHER INSTRUCTIONS.

DO YOU -- DO YOU UNDERSTAND WHAT THAT STANDARD IS AND WHETHER IT'S BEEN PROPERLY ARTICULATED BY MR. PASAHOW?

THE WITNESS: I DON'T FULLY UNDERSTAND HIS QUESTION, NO.

Q. (BY MR. PASAHOW) WELL, THE QUESTION, SIR, TO PUT IT THE WAY THAT JUDGE PATEL SUGGESTS, IS: WHAT STANDARD DO YOU BELIEVE THE EXAMINER WAS APPLYING WHEN HE FOUND THAT THE DU PONT REQUEST FOR RE-EXAMINATION SHOULD NOT GO FORWARD ON THE '195 PATENT AS TO THE CLAIMS THAT ARE INVOLVED IN THIS CASE?

A. I THOUGHT THAT THE STANDARD WOULD BE WHETHER THE PRIOR ART TAUGHT THE CLAIMS IN QUESTION.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) DID YOU DISTINGUISH, IN THINKING ABOUT THAT, BETWEEN THE QUESTION WHETHER THE PRIOR ART AS A -- AS A COLLECTION WOULD HAVE MADE THE CLAIM OBVIOUS, ON THE ONE HAND, FROM WHETHER SOME SINGLE PIECE OF PRIOR ART CONTAINED WITHIN IT ALL OF THE ELEMENTS OF THE CLAIM?

A. YOU'RE SPEAKING ABOUT THE '195 PATENT NOW.

Q. YES.

A. I WAS ASKING MYSELF WHAT ONE OF ORDINARY SKILL IN THE ART WOULD HAVE KNOWN IN 1984, AND WHETHER THAT WAS TAUGHT -- WHETHER THAT MADE THE CLAIM OBVIOUS.

Q. SO YOU WERE TRYING TO FIGURE OUT WHETHER THE EXAMINER CORRECTLY DECIDED WHETHER THE CLAIMS WERE OBVIOUS IN LIGHT OF ALL OF THE PRIOR ART.

A. I WAS TRYING TO DETERMINE WHETHER ONE OF ORDINARY SKILL WOULD HAVE BEEN ABLE TO PRACTICE THE CLAIM IN 1984.

(PAUSE IN PROCEEDINGS)

THE WITNESS: I'VE ALREADY SAID THAT -- THAT THE PRIOR ART ON AMPLIFICATION WAS IN THE KHORANA PRIOR ART AND THE HYBRIDIZATION PRIOR ART -- OR THE HYBRIDIZATION WAS WELL KNOWN IN 1984.

Q. (BY MR. PASAHOW) SO SOMEONE WOULD HAVE HAD TO HAVE GONE TO SEPARATE SOURCES TO FIND OUT HOW TO DO THIS, IN YOUR OPINION.

A. WELL, THAT PERSON SHOULD NOT HAVE HAD TO GO TO A SOURCE. I MEAN, THEY SHOULD HAVE KNOWN THAT. I MEAN, I -- I'M SAYING THAT THE PERSON OF ORDINARY SKILL WOULD HAVE KNOWN THAT IN 1984.

Q. WOULD HAVE KNOWN BOTH HOW TO DO THE AMPLIFICATION AND HOW TO DO THE HYBRIDIZATION.

A. GIVEN THE KHORANA PRIOR ART --

Q. UH-HUH.

A. -- THEY WOULD HAVE KNOWN HOW TO PERFORM THE HYBRIDIZATION STEPS BECAUSE THAT WAS WHAT SCIENTISTS DID IN THOSE DAYS, AND STILL TODAY.

Q. DID YOU TRY AND FIGURE OUT HOW THE EXAMINER CAME TO HIS DECISION?

(PAUSE IN PROCEEDINGS)

THE WITNESS: I . . . UNDERSTOOD -- WELL, I JUST THINK HIS DECISION WAS WRONG.

Q. (BY MR. PASAHOW) DID YOU TRY AND FIGURE OUT HOW HE CAME TO IT?

(PAUSE IN PROCEEDINGS)

THE WITNESS: WELL, I DON'T QUITE KNOW WHAT YOU MEAN.

Q. (BY MR. PASAHOW) WELL, DID YOU, FOR EXAMPLE, EXAMINE THE SUBMISSIONS THAT WERE MADE TO THE PATENT OFFICE?

A. I HAVE LOOKED AT THEM.

Q. DID -- DID YOU READ --

A. SOME OF THEM.

Q. DO I TAKE IT FROM THAT THAT YOU DID NOT READ THROUGH ALL OF THEM?

A. WELL, I WAS BASING MY DECISION ON THE PRIOR ART REFERENCES THAT I LOOKED AT, SO MY OPINION'S BASED ON WHAT I LOOKED AT, AND

I LOOKED AT OTHER ARGUMENTS AND THOSE ARGUMENTS HADN'T CONVINCED ME OTHERWISE.

Q. SO YOU DID NOT LOOK AT WHAT DU PONT PUT IN FRONT OF THE EXAMINER FOR THE EXAMINER'S DECISION SPECIFICALLY.

A. I LOOKED AT -- AT AT LEAST SOME OF THE -- THOSE THINGS, YEAH.

Q. NOW, AS TO THE '202 PATENT, THE BASIC AMPLIFICATION PATENT --

A. UH-HUH.

Q. -- YOU UNDERSTAND THAT THE EXAMINER FOUND THAT NONE OF THE CLAIMS IN THAT PATENT WERE OBVIOUS.

(PAUSE IN PROCEEDINGS)

THE WITNESS: I DON'T KNOW IF OBVIOUS WAS A QUESTION IN THAT PARTICULAR PATENT.

Q. (BY MR. PASAHOW) WELL, YOU'RE AWARE THAT DU PONT ASKED THE EXAMINER TO REVIEW THE PATENT AND SEE IF ANY OF THE ART MADE THE CLAIMS OBVIOUS.

A. WELL, AGAIN, WHAT I'M TRYING TO SAY IS, IS THAT I . . . I'M REALLY TESTIFYING TO THE WAY I WOULD HAVE -- I VIEWED THE -- THE RELEVANT PRIOR ART, THE KHORANA PRIOR ART, WITH RESPECT TO WHETHER THAT'S IN THE CLAIM. THAT'S -- THAT WAS MY STANDARD: IS THE CLAIM THE SAME THING AS THE PRIOR ART?

Q. WELL, SIR, YOU TOLD THE COURT THAT YOU THOUGHT THE EXAMINER'S DECISION WAS WRONG.

A. WITH RESPECT TO THE '195 PATENT, YES.

Q. YES.

AND WHAT I'M TRYING -- AND YOU SAID THAT YOU THOUGHT IT WAS WRONG IN PART BECAUSE YOU THOUGHT IT WAS INCONSISTENT WITH THE EXAMINER'S DECISION IN THE '202 PATENT.

A. WELL, I UNDERSTOOD THAT THE EXAMINER FOUND A QUESTION OF PATENTABILITY IN THE '202 PATENT.

Q. YES.

DID HE FIND THAT ANY OF THE CLAIMS IN THE '202 PATENT SHOULD BE EXAMINED BECAUSE THEY MIGHT BE OBVIOUS?

A. I DON'T REMEMBER WHAT THE ISSUES WERE, OBVIOUS OR ANTICIPATED.

Q. WELL, ISN'T IT TRUE THAT THE ONLY QUESTION THAT THE EXAMINER FOUND MERITED FURTHER CONSIDERATION AS TO THE '202 PATENT WAS WHETHER SOME OF THE CLAIMS WERE ANTICIPATED?

A. WELL, I WOULD . . . I THOUGHT ANTICIPATION WAS THE ISSUE, YES.

Q. YES.

AND AS TO BOTH THE '202 PATENT AND THE '195 PATENT, THE EXAMINER CONSISTENTLY FOUND THAT NO CLAIM WAS OBVIOUS.

(PAUSE IN PROCEEDINGS)

THE WITNESS: WITH RESPECT TO -- I DON'T UNDERSTAND. WITH RESPECT TO THE '195 PATENT, HE FOUND THAT NO CLAIM WAS OBVIOUS, THAT'S TRUE.

Q. (BY MR. PASAHOW) AND THAT'S WHAT HE FOUND IN HIS VERY FIRST STEP AS TO THE '202 PATENT AS WELL.

A. RIGHT -- WELL, IF THE TWO -- IF THE '202 PATENT -- ANY CLAIM IN THE '202 PATENT WERE OB -- WERE ANTICIPATED, AND ONE OF ORDINARY SKILL IN 1984 COULD HAVE DETERMINED THE REST OF THOSE STEPS, THEN THEY WOULD HAVE BEEN OBVIOUS.

Q. YES, SIR. WE'RE TALKING ABOUT WHAT THE EXAMINER FOUND.

A. UH-HUH.

Q. AND IT'S TRUE THAT, AS TO THE '202 PATENT, THE PATENT THAT HAS TO DO WITH THE BASIC AMPLIFICATION PROCESS, THE PATENT EXAMINER FOUND IN THIS VERY FIRST STEP THAT NO CLAIM IN IT WAS OBVIOUS IN LIGHT OF THE KHORANA REFERENCES; ISN'T THAT RIGHT?

A. I DON'T KNOW THAT HE EXAMINED OBVIOUSNESS. I THINK ANTICIPATION WAS WHAT HE WAS . . . LOOKING AT.

Q. WELL, DO YOU KNOW WHETHER OR NOT DU PONT ASKED THAT HE LOOK AT THE OBVIOUSNESS QUESTION --

A. I DON'T.

Q. -- AS TO THE AMPLIFICATION PROCESS?

A. I DON'T RECALL.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) ARE YOU RECEIVING COMPENSATION FROM DU PONT FOR YOUR WORK WITH IT IN THIS CASE?

A. NOT DIRECTLY. ACTUALLY, THE ARRANGEMENT IS BETWEEN CITY OF HOPE AND DU PONT, AND COMPENSATION GOES TO THE CITY OF HOPE FOR MY ACTIVITIES.

Q. DO YOU RECEIVE THAT SOMEHOW?

A. IT GOES INTO AN ACCOUNT AT THE CITY OF HOPE, WHICH IS

A . . . I THINK IT'S CALLED AN ACADEMIC IMPROVEMENT ACCOUNT, WHICH CAN BE USED FOR RESEARCH ACTIVITIES, TRAVEL, THAT KIND OF THING. AND I CAN RECEIVE FROM THAT ACCOUNT, WHICH -- FROM WHICH MANY SOURCES MIGHT HAVE CONTRIBUTED, $5,000 A YEAR.

Q. NOW, WHY DID YOUR EMPLOYER JOIN WITH DU PONT IN MAKING YOUR SERVICES AVAILABLE?

A. I DON'T KNOW WHAT . . . YOU KNOW, EXACTLY WHY MY EMPLOYER MADE THAT DECISION.

Q. WELL, ISN'T THE CITY OF HOPE THE PERSON THAT OWNS SEVERAL PATENTS OR SEVERAL PATENT APPLICATIONS INVOLVING THE PCR PROCESS?

A. WELL, PERHAPS I SHOULD EXPLAIN WHY OUR ORGANIZATION WOULD HAVE PATENTS -- PATENTS OR PATENT APPLICATIONS AT ALL.

Q. WELL, I'D RATHER YOU TOLD ME WHETHER OR NOT IT'S TRUE THAT THE CITY OF HOPE HAS OWNERSHIP OF SEVERAL PATENT APPLICATIONS INVOLVING THE PCR PROCESS.

A. YES, THAT'S TRUE.

Q. AND AS TO THOSE APPLICATIONS, YOU ARE AN INVENTOR ON EACH OF THEM?

A. I DON'T KNOW THAT I'M INVENTOR IN ALL OF THEM.

Q. ON SEVERAL OF THEM, YOU'RE AN INVENTOR.

A. ON SEVERAL, YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, AT LEAST ONE OF THOSE PATENT APPLICATIONS IN WHICH YOU'RE AN INVENTOR AND THAT'S OWNED BY THE

CITY OF HOPE, IT CLAIMS SOMETHING THAT IS IDENTICALLY COVERED IN THE '195 DETECTION PATENT; IS THAT RIGHT?

A. WELL, THAT PATENT APPLICATION YOU'RE REFERRING . . .

(MR. FIGG RISES.)

THE COURT: YES?

MR. FIGG: EXCUSE ME, YOUR HONOR. IF MR. PASAHOW IS GOING TO ASK THE WITNESS ABOUT SPECIFIC PATENT APPLICATIONS, I THINK THE WITNESS SHOULD BE SHOWN COPIES -- A COPY OF THE PARTICULAR APPLICATION THAT THE QUESTION IS DIRECTED TO.

THE COURT: WELL, I THINK THAT OBJECTION IS WELL TAKEN IF HE SAYS HE DOESN'T RECALL AND NEEDS TO LOOK AT -- AT THE APPLICATION. IF HE HAS AN INDEPENDENT RECOLLECTION WITHOUT REVIEWING IT, THEN HE MAY ANSWER.

CAN YOU ANSWER THE QUESTION WITHOUT --

THE WITNESS: WELL, IT'S CONCEIVABLE WE'RE TALKING ABOUT A DIFFERENT PATENT APPLICATION, BUT . . .

THE COURT: DO YOU KNOW THEM BY THEIR COMMONLY-USED THREE DIGITS OR --

(LAUGHTER)

THE WITNESS: NO, I DON'T.

Q. (BY MR. PASAHOW) DR. WALLACE, I DON'T WANT YOU TO BE GUESSING. LET ME SHOW YOU WHAT WE'VE MARKED AS EXHIBIT B-187.

A. (WITNESS EXAMINES DOCUMENT.)

MR. FIGG: YOUR HONOR, WE HAVE COPIES THAT COUNSEL HAS KINDLY PROVIDED US, BUT THEY DON'T HAVE THE EXHIBIT NUMBERS ON

THEM.

THE COURT: OKAY. WOULD YOU REFER TO THE PATENT NUMBER FOR THEM?

MR. PASAHOW: YES, YOUR HONOR.

MR. FIGG: THANK YOU.

MR. PASAHOW: THIS IS PATENT NUMBER 143,045, WHICH WAS FILED ON JULY 12, 1988.

THE WITNESS: YES, SIR.

Q. (BY MR. PASAHOW) YOU'RE AN INVENTOR ON THIS PATENT?

A. YES, I AM.

Q. AND YOU SIGNED A DECLARATION IN CONNECTION WITH THAT APPLICATION; IS THAT CORRECT?

A. YES.

Q. YOU SIGNED THAT IN MARCH 1988?

(PAUSE IN PROCEEDINGS)

THE WITNESS: YES.

Q. (BY MR. PASAHOW) AND IN THAT DECLARATION, YOU SAID THAT YOU BELIEVED YOU WERE AN ORIGINAL FIRST AND JOINT INVENTOR OF THE SUBJECT MATTER OF THE PATENT APPLICATION.

A. (WITNESS EXAMINES DOCUMENT.) YES.

Q. AND YOU SAID THAT YOU HAD REVIEWED AND UNDERSTOOD THE CONTENTS OF THE APPLICATION.

A. YES.

Q. INCLUDING THE SPECIFICATION OF THE APPLICATION.

A. YES.

Q. AND THE CLAIMS.

A. YES.

Q. AND YOU ACKNOWLEDGE THAT YOU HAD A DUTY TO DISCLOSE TO THE PATENT OFFICE INFORMATION WHICH WAS MATERIAL TO THE APPLICATION.

A. I SUPPOSE THAT SAYS THAT IN HERE SOMEWHERE. I . . . YES.

Q. DO YOU SEE THAT?

A. NO, I DON'T. COULD YOU . . .

Q. (INDICATING.)

A. OKAY. UH-HUH.

Q. SO YOU DID ACKNOWLEDGE YOUR DUTY TO DISCLOSE INFORMATION WHICH IS MATERIAL TO THE EXAMINATION OF THE APPLICATION.

A. YES.

Q. AND, FINALLY, YOU DECLARED THAT ALL OF THE STATEMENTS WERE MADE -- ALL OF THE STATEMENTS MADE WERE TRUE AND CORRECT.

A. YES.

Q. NOW, THIS PATENT APPLICATION, EXHIBIT B-187, COVERS --

A. UH-HUH.

Q. -- A SUBJECT MATTER WHICH IS IDENTICAL TO A PART OF THE '195 PATENT; IS THAT RIGHT?

A. WELL, FIRST, YOU MUST REALIZE THAT THIS PATENT APPLICATION WAS ORIGINALLY FILED BEFORE THE '195 PATENT ISSUED, SO I HAD NO KNOWLEDGE OF THE '195 PATENT WHEN THE SPECIFICATION WAS ORIGINALLY WRITTEN IN DECEMBER OF 1986.

AND SO . . . THE '195 PATENT HAS WITHIN IT THE -- THE IDEAS THAT YOU CAN AMPLIFY AN RNA AND DETECT IT WITH A PROBE,

THAT'S CORRECT.

IT WAS MY IMPRESSION THAT TO APPLY A SPECIFIC SET OF CONDITION -- OF CONDITIONS FOR AN EXPERIMENT, PARTICULAR SETS OF PRIMERS AND PROBES, FOR SOMETHING AS IMPORTANT AS AN AIDS TEST WOULD HAVE BEEN INVENTIVE, SO WE FILED THIS APPLICATION.

WE WERE BASING OUR ORIGINAL EXPERIMENTS ON THE SAIKI PAPER, WHICH WAS PUBLISHED IN 1985, WHICH DIDN'T MENTION REVERSE TRANSCRIPTASE OR DIDN'T HAVE EXPERIMENTS IN REVERSE TRANSCRIPTASE.

SO THIS APPLICATION THEN WAS RE-FILED IN 1988. I THINK THAT'S WHAT IT'S CALLED, CONTINUATION-IN-PART. ISN'T THAT WHAT IT'S CALLED?

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) WELL, LET'S . . . LET'S PUT THE CLAIM UP SO WE CAN ALL SEE IT HERE.

NOW, DO YOU UNDERSTAND THAT CLAIM TO BE LIMITED TO DETECTING THE HIV VIRUS?

A. WELL, NO, BUT THIS PATENT APPLICATION HAS BEEN IN -- THIS APPLICATION'S BEEN ABANDONED.

Q. YES, SIR. BUT WHEN YOU FILED IT IN MARCH 1988, YOU FILED THE PATENT APPLICATION SEEKING TO PATENT THE USE OF PCR ON ALL RNA AMPLIFICATION AND DETECTION; IS THAT CORRECT?

A. OH, I THINK I UNDERSTAND YOUR QUESTION. I WAS . . .

I DON'T KNOW HOW THE LEGAL PROCESS WORKS EXACTLY, BUT WHAT -- WHAT I UNDERSTAND IS THAT, IN ORDER TO KEEP AN

APPLICATION GOING, YOU'RE -- YOU'RE -- THE PATENT ATTORNEYS RE-FILE LIKE THIS CONTINUATION-IN-PART BUSINESS WITH THE SAME SPECIFICATION AND THE SAME CLAIM AS WAS FILED IN 1986.

SO IN 1986, WE DIDN'T KNOW ABOUT THE '195 PATENT, SO THE -- THE SPECIFICATION CLAIMS ARE BASED ON THE ONE -- NOT -- THAT GOES BACK TO 1986.

Q. LET'S SEE IF WE CAN BREAK THIS DOWN:

THIS PATENT HAS ONE CLAIM IN IT; IS THAT RIGHT?

A. RIGHT. THIS . . . BUT IT'S SINCE BEEN ABANDONED, YES.

Q. THIS PATENT APPLICATION, THOUGH, INVOLVED A SINGLE CLAIM.

A. YEAH, SINGLE CLAIM.

Q. AND THAT SINGLE CLAIM WAS A VERY BROAD CLAIM FOR THE USE OF PCR TO DETECT ANY RNA SEQUENCE.

A. THAT'S CORRECT.

Q. AND IN MARCH 1988, YOU THOUGHT THAT WAS A NEW AND NOVEL INVENTION.

A. WELL, I'M TRYING TO EXPLAIN TO YOU THAT REALLY THE WAY I UNDERSTOOD THE PROCESS, THIS IS THE SPECIFICATION AS WRITTEN IN 1986; OKAY? AND IT WAS SIMPLY RE-FILED IN ESSENTIALLY THE SAME FORM, I GUESS IDENTICAL FORM, AS IT WAS FILED IN 1986 AS A CONTINUATION-IN-PART.

Q. WHEN THIS APPLICATION WAS FILED IN MARCH 1988, DID YOU BELIEVE THAT WHAT YOU CLAIMED TO THE PATENT OFFICE AS A NEW AND NOVEL INVENTION WAS A NEW AND NOVEL INVENTION?

A. THE CLAIM WAS SINCE -- I MEAN, THE APPLICATION WAS SINCE

ABANDONED.

Q. SIR, IN MARCH 1988, WHEN YOU FILED IT, AND DECLARED UNDER OATH THAT YOU WERE AN INVENTOR AND THOUGHT YOURSELF TO BE ONE, DID YOU BELIEVE THIS CLAIM WAS A NEW AND NOVEL INVENTION?

A. THIS -- I'M JUST TRYING TO EXPLAIN: THAT'S WHAT I THOUGHT WHEN I FILED IT IN 1986.

Q. THIS -- THIS IDENTICAL CLAIM WAS FILED IN 1986?

A. AS FAR AS I KNOW.

Q. AND THEN YOU RE-FILED THE SAME CLAIM IN MARCH 1988.

A. RIGHT. ON ADVICE OF COUNSEL, THEY RE-FILED -- I MEAN, I HAVE VERY LITTLE TO DO WITH THESE THINGS. THEY RE-FILE IT. THEY TELL ME THAT THIS IS THE WAY YOU RE-FILE A CONTINUATION-IN-PART.

Q. NOW, WHEN YOU FILED THE CONTINUATION-IN-PART, YOU SIGNED A NEW OATH TO THE PATENT OFFICE.

A. APPARENTLY, YES.

Q. WELL, NOT APPARENTLY. ISN'T THAT IN THE FRONT PAGE OF THIS EXHIBIT?

A. WELL, YOU . . . THE SPECIFICATION DESCRIBES A TEST FOR DETECTING THE AIDS VIRUS; OKAY? AND THAT IS INVENTIVE, I BELIEVE.

THE CLAIM IS A CLAIM THAT IS . . . IT SAYS:

"A PROCESS FOR THE RAPID AMPLIFICATION AND DETECTION OF RNA SEQUENCE WHICH COMPRISES:

"ADDING TO RNA TWO CONVERGING

OLIGODEOXYRIBONUCLEOTIDE PRIMERS AT LEAST ONE OF WHICH IS COMPLEMENTARY TO SEQUENCE INCLUDING -- INCLUDED IN SAID RNA;

"THEREAFTER EXTENDING AT LEAST ONE OF SAID PRIMERS WITH ONE OR BOTH REVERSE TRANSCRIPTASE AND DNA POLYMERASE; AND

"DETERMINING WHETHER SAID SEQUENCE IS PRESENT IN SAID AMPLIFIED SEGMENT BY USE OF SYNTHETIC OLIGODEOXYRIBONUCLEOTIDE PROBE COMPLEMENTARY TO A SEQUENCE WITHIN THE SEGMENT."

AND . . . THAT WAS THE BASIS FOR THE PATENT APPLICATION. AND I THOUGHT THAT AT THAT TIME, IN 1986, AT LEAST, THAT WE HAD AN INVENTION.

Q. AND THAT WAS AFTER YOU HAD READ THE CETUS PUBLICATIONS?

A. AFTER I'D READ THE 1985 PUBLICATION.

Q. THAT'S WHAT YOU REFER TO AS SAIKI?

A. YES.

Q. AND THAT TOLD YOU HOW TO DO A PCR AMPLIFICATION?

A. IT TOLD ME HOW TO AMPLIFY DNA.

Q. NOW, THE WORDS YOU READ FOR YOUR CLAIM, IS THERE A CLAIM IN THE CETUS '195 PATENT WHICH COVERS THE SAME THING?

A. THE '195 PATENT COVERS, AS I UNDERSTAND IT, CONVERTING A DNA -- AN RNA TO A DNA AND THEN USING IT IN AMPLIFICATION.

Q. AND DOES YOUR PROCESS PROPOSE CONVERTING THE RNA TO A DNA AND USING IT IN AMPLIFICATION?

A. (WITNESS EXAMINES DOCUMENT.) YES.

Q. SO IT COVERS THE SAME THING.

A. YES. AS I TOLD YOU, WE'VE ABANDONED THIS PATENT APPLICATION.

Q. YOU ABANDONED IT.

A. WELL, AS FAR AS I KNOW.

Q. NOW, IS THE CETUS CLAIM WHICH COVERS THE SAME THING AS THE CLAIM THAT YOU TOLD THE PATENT OFFICE IN 1988 WAS A NEW AND NOVEL INVENTION, IS THAT CLAIM A NEW AND NOVEL INVENTION?

A. I DON'T THINK SO NOW.

Q. AND WHY NOT?

A. BECAUSE YOU COULD -- YOU KNOW, NOW THAT I'VE READ THE KHORANA PRIOR ART, AND WHAT I KNEW . . . AND FROM WHAT I'VE KNOWN -- WHAT I KNEW IN 1984, IT WOULD HAVE BEEN OBVIOUS.

Q. NOW, LET'S SEE IF I UNDERSTAND THAT:

IN 1988, WHEN YOU FILED THIS, YOU KNEW ABOUT THE CETUS ARTICLES DESCRIBING IN DETAIL THE PCR PROCESS, AND YOU KNEW ABOUT DETECTION; IS THAT RIGHT?

A. UH-HUH. YES, THAT'S CORRECT.

Q. AND, AT THAT TIME, YOU THOUGHT DETECTING AN RNA SEQUENCE WAS A NEW AND NOVEL INVENTION WORTHY OF A PATENT?

A. WELL, THE PROCESS IS A LITTLE BIT DIFFERENT THAN THAT, I THINK.

WE DISCLOSE OUR IDEAS TO OUR OFFICE OF SPONSOR RESEARCH, WHOSE JOB IT IS TO PROVIDE INCOME TO THE CITY OF HOPE

TO CONDUCT OUR BASIC RESEARCH. AND ONE OF THE WAYS THEY DO THAT IS TO TRY TO PROTECT OUR INTELLECTUAL PROPERTY THROUGH A PATENT PROCESS. WE'RE NOT A COMPANY, BUT WE DO NEED TO PROTECT OUR INTELLECTUAL PROPERTY AS A WAY OF SUPPORTING RESEARCH.

AND SO I PRESENT -- OR WE, THE INVENTOR -- INVESTIGATORS, PRESENT THESE IDEAS TO THE OFFICE OF SPONSOR RESEARCH. HE PRESENTS IT TO PATENT COUNSEL. PATENT COUNSEL MAKES DECISIONS AS TO WHETHER THERE IS INVENTIVENESS OR AN INVENTION INVOLVED AND FILES A PATENT APPLICATION ON OUR BEHALF.

THE . . . THE . . . COUNSEL IS THE ONE WHO'S REALLY SAYING THIS IS INVENTIVE BECAUSE IT DOESN'T COVER THE PRIOR ART, WHICH HE'S LOOKED AT.

Q. SIR --

A. WE JUST SIMPLY HAD DONE AN AIDS TEST, AND THAT'S WHAT WE PRESENTED TO HIM.

Q. DID ANYONE TELL YOU TO FILE A DECLARATION THAT YOU DIDN'T BELIEVE WAS TRUE?

A. NO.

Q. SO WHEN YOU SIGNED THE DECLARATION, YOU CERTAINLY THOUGHT IT WAS TRUE.

A. AT THAT TIME?

Q. YES.

A. IN 1986?

Q. IN -- NO.

SIR, WHEN YOU SIGNED THIS DECLARATION IN MARCH 1988,

DID YOU BELIEVE IT WAS TRUE?

A. THAT I HAD READ IT, AND I UNDERSTOOD IT, AND THAT I'M THE ORIGINAL INVENTOR, YES.

Q. YES. THE ORIGINAL INVENTOR.

A. I DIDN'T SIGN A DECLARATION THAT SAID I -- THAT I BELIEVED IT WAS AN INVENTION. I SIGNED IT . . . BECAUSE THAT'S REALLY SORT OF IN BETWEEN -- I MEAN, WE'RE GOING TO GO TO THE PATENT OFFICE. WE DIDN'T GET A PATENT ON THIS.

SO I SAID I BELIEVE I AM THE ORIGINAL, FIRST AND SOLE INVENTOR.

Q. YES.

A. THAT DOESN'T NECESSARILY MEAN I'M -- I BELIEVE IT'S AN INVENTION.

Q. I SEE.

A. THIS IS A PATENT APPLICATION.

Q. SO YOU --

A. AND THAT I -- THAT I UNDERSTOOD IT, AND THAT I HAD READ IT.

Q. YOU WERE THE INVENTOR OF THIS, BUT YOU DIDN'T THINK IT WAS AN INVENTION.

A. WELL, I THINK THAT'S FOR THE PATENT OFFICE TO DECIDE, OR FOR OTHER INDIVIDUALS TO DECIDE.

Q. DID YOU THINK IT WAS OBVIOUS TO ONE ORDINARILY SKILLED IN THE ART WHEN YOU FILED IT?

A. WE DID A SET OF EXPERIMENTS AND PRESENTED IT TO THE PATENT OFFICE. THEY CONSIDERED IT OBVIOUS, YES. THEY CONSIDERED IT

OBVIOUS.

Q. YES.

A. AND WE'VE ABANDONED THE PATENT APPLICATION.

Q. THEY CONSIDERED IT OBVIOUS BECAUSE OF THE CETUS ART; IS THAT RIGHT?

A. I DON'T REMEMBER EXACTLY WHICH -- AND WHAT -- I DON'T REMEMBER WHEN THE FIRST -- WHETHER THERE WAS AN OFFICE ACTION OR . . . ON THE ORIGINAL APPLICATION OR ON THIS APPLICATION. SO I DON'T KNOW WHETHER THEY WERE, FOR EXAMPLE, USING '195 OR WHETHER THEY WERE USING THE CETUS ART.

Q. BY '195, YOU MEAN THE CETUS PATENT.

A. YES.

Q. SO YOU'RE SAYING THAT IT WAS OBVIOUS EITHER BECAUSE OF THE CETUS PATENT OR THE CETUS ART.

A. YES, SO WE'VE ABANDONED THIS.

Q. YES.

NOW LET'S GO BACK TO MARCH 1985, SIR, WHEN YOU FILED IT WITH THE PATENT OFFICE:

YOU FILED A PARTICULAR CLAIM HERE, AND YOU'VE SHOWN THAT YOU'RE VERY GOOD AT READING CLAIMS, AS YOU'VE GONE THROUGH MANY WITH MR. FIGG.

A. YES.

Q. NOW, WHEN YOU READ THIS CLAIM AND YOU TOLD THE PATENT OFFICE THAT YOU THOUGHT YOU WERE THE INVENTOR OF IT, DID YOU THINK THAT THE CLAIM WAS SOMETHING THAT WAS OBVIOUS TO THE

ORDINARILY-SKILLED PERSON?

A. THE CLAIM WAS WRITTEN BY AN ATTORNEY WHO TOLD ME THAT THIS WAS INVENTIVE BECAUSE OF THE PRIOR ART HE HAD LOOKED AT. WE DISCUSSED THE PRIOR ART TOGETHER, AND HE PUTS IT TOGETHER AS A BROAD CLAIM THAT HE SUBMITTED TO THE PATENT OFFICE. THAT CLAIM IS OBVIOUS, AND WE HAVE ABANDONED THE PATENT APPLICATION.

Q. SIR, I'M TRYING TO ASK A SPECIFIC QUESTION, AND I'D APPRECIATE AN ANSWER, AND THAT IS, IN MARCH 1988 --

A. UH-HUH.

Q. -- WHEN YOU FILED THIS CLAIM, DID YOU THINK THE SUBJECT MATTER OF THE CLAIM WAS OBVIOUS TO ONE ORDINARILY SKILLED IN THE ART?

A. I DON'T RECALL WHAT I THOUGHT AT THAT TIME. I WAS TOLD THAT THIS IS A STANDARD PRACTICE OF PATENT LAW WHERE YOU SIMPLY RE-FILE THE SAME APPLICATION AS WAS PREVIOUSLY FILED AND . . . AND RESUBMIT IT AS A CONTINUATION-IN-PART.

I SIGNED THIS, THAT I HAD READ IT AND I UNDERSTOOD IT, AND THAT I WAS THE ORIGINAL INVENTOR, BECAUSE THIS IS A PATENT APPLICATION --

Q. UH-HUH.

A. -- OKAY? PATENT APPLICATIONS HAVE INVENTORS.

Q. YES.

A. THAT DOESN'T NECESSARILY MEAN I BELIEVED THAT IT WAS NOT OBVIOUS AT THAT TIME. I DIDN'T MAKE ANY STATEMENTS ABOUT OBVIOUSNESS.

Q. WELL, WHEN YOU FILED THE ORIGINAL ONE OF THESE IN 1986, AGAIN AFTER YOU READ THE CETUS ART AND, OF COURSE, KNEW ABOUT PROBING AND DETECTION, AT THAT TIME, DID YOU THINK THAT WHAT YOU WERE CLAIMING WAS OBVIOUS TO ONE ORDINARILY SKILLED IN THE ART?

A. AGAIN, THAT WAS A DECISION -- A DECISION THAT IT -- IT'S A LEGAL DECISION THAT OUR PATENT ATTORNEY MADE WHEN HE WROTE THE CLAIM.

WE PRESENTED TO HIM THE EXPERIMENTS WE DID. WE DID EXPERIMENTS TO DETECT THE AIDS VIRUS. THE SAIKI ARTICLE DIDN'T DESCRIBE DOING THAT. HE CHOSE TO WROTE A BROAD -- WRITE A BROAD CLAIM COVERING RNA, TURNING RNA INTO DNA, AND DETECTING IT BY HYBRIDIZATION, WHICH IS IN THE '195 PATENT. THAT IS OBVIOUS, YES.

Q. I DON'T SEE WHY YOU SAY THAT'S A LEGAL DETERMINATION. YOU'D BEEN THROUGH SOME 20 CLAIMS HERE WITH MR. FIGG GIVING US YOUR TECHNICAL EVALUATION THAT THINGS ARE OBVIOUS IN LIGHT OF PRIOR ART.

THE QUESTION IS: WHEN YOU FILED THIS IN 1986, ARE YOU TELLING US THAT IN 1986 WHEN YOU FILED IT, YOU THOUGHT IT WAS SOMETHING THAT WOULD HAVE BEEN OBVIOUS TO ONE ORDINARILY SKILLED IN THE ART, AND YOU SIGNED THE -- THE DECLARATION, ANYWAY?

A. IT WAS MY POSITION THAT AN AIDS TEST WAS NOVEL. THAT'S WHAT'S IN THE SPECIFICATION. THIS IS A CLAIM TO SUPPORT THAT, BUT IT'S A VERY BROAD CLAIM.

Q. UH-HUH.

A. I DIDN'T THINK THE AIDS TEST WAS OBVIOUS. THE BROAD CLAIM IN LIGHT OF WHAT WE'VE BEEN TALKING ABOUT IS OBVIOUS. WHETHER THE AIDS TEST IS OBVIOUS, I DON'T THINK SO, BUT THAT'S ANOTHER ISSUE.

Q. SIR, THE QUESTION WAS: BACK IN 1986 --

A. UH-HUH.

Q. -- WHEN YOU SWORE TO THE PATENT OFFICE THAT YOU WERE THE INVENTOR, DID YOU THEN THINK THAT THE CLAIM WAS OBVIOUS TO ONE ORDINARILY SKILLED IN THE ART?

A. I SWORE I WAS AN INVENTOR AND THAT I UNDERSTOOD THIS, AND WE PRESENTED THIS TO THE PATENT OFFICE AS A BROAD CLAIM TO SUPPORT THE SPECIFICATION. THE PATENT OFFICE FOUND IT WAS OBVIOUS.

Q. UH-HUH.

A. WE WOULD -- IN -- IN THE NEGOTIATION, YOU WOULD WRITE A NEW CLAIM THEN, PERHAPS BE A MORE LIMITED CLAIM. IT WAS OBVIOUS.

Q. I DON'T KNOW IF I CAN PUT THIS ANY MORE PLAINLY, SIR.

THE QUESTION IS: WHEN YOU SIGNED THE OATH TO THE PATENT OFFICE, DID YOU BELIEVE THAT IT WAS KNOWN TO ONE ORDINARILY SKILLED IN THE ART?

A. I KNEW IT.

Q. I SEE.

A. AND . . .

Q. NOW, AS WE READ THIS CLAIM --

A. UH-HUH.

Q. -- DO YOU THINK THIS CLAIM WOULD EXPLAIN TO SOMEONE HOW TO

DO THE PROCESS THAT YOU SET OUT IN THE SPECIFICATION OF THE PATENT?

A. (WITNESS EXAMINES DOCUMENT.)

(PAUSE IN PROCEEDINGS)

MR. FIGG: OBJECT TO THE RELEVANCY OF THAT QUESTION, YOUR HONOR. IT'S NOT THE PURPOSE OF THE CLAIM TO DESCRIBE HOW TO DO THE PROCESS. IT'S TO DEFINE THE PROCESS AND TO DEFINE THE SCOPE OF THE INVENTION.

THE COURT: WELL, YOU'RE OBJECTING, THEN, TO THE PHRASING OF THE QUESTION.

MR. FIGG: I'M OBJECTING TO THE RELEVANCE OF THE QUESTION. I CAN'T SEE ANY POSSIBLE RELEVANCE TO THAT QUESTION.

THE COURT: THE OBJECTION IS OVERRULED.

YOU MAY ANSWER THE QUESTION.

THE WITNESS: WELL, THE CLAIM DESCRIBED THE . . . WHAT THE -- WHAT THE PROCESS COVERED, CONVERTING AN RNA TO A DNA --

Q. (BY MR. PASAHOW) UH-HUH.

A. -- AMPLIFYING IT AND DETECTING IT.

Q. DID YOU THINK THERE WAS ENOUGH DETAIL IN THE CLAIM TO EXPLAIN TO SOMEONE HOW TO DO WHAT IT WAS YOU WERE CLAIMING?

A. ONE OF ORDINARY SKILL?

Q. YES, SIR.

A. THE CLAIM WAS JUST COVERING THE GROUND THAT THE PATENT -- THAT THE -- THAT WAS COVERED BY THE -- BY THAT.

Q. SO SOMEONE OF ORDINARY SKILL WOULD HAVE HAD TO HAVE GONE TO

THE SPECIFICATION TO FIND OUT THE DETAILS OF HOW TO DO WHAT IS COVERED BY THE CLAIM; IS THAT RIGHT?

A. YES, I GUESS THAT WOULD BE FAIR TO SAY.

Q. AND IS THAT HOW YOU UNDERSTAND A PATENT WORKS, THAT IS, THE CLAIM DESCRIBES THINGS IN VERY BROAD, GENERAL LANGUAGE, AND THE SPECIFICATION CONTAINS THE DETAILS ABOUT HOW TO DO IT?

A. WELL, THE CLAIM COVERS THE AREA THAT -- OF THE INVENTION, KIND OF LIKE THE DEED ANALOGY THAT MR. DE GRANDI USED, I THINK, OR WE'VE HEARD. I DON'T KNOW. SO IT COVERS THE AREA. AND THE SPECIFICATION HAS DETAILS ON SOME -- ON THE PROCESS.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, IN CONNECTION WITH THIS PATENT APPLICATION, B-187, DID YOU PROVIDE THE PATENT OFFICE WITH A COPY OF ANY OF THE KHORANA REFERENCES?

A. NO. I WAS UNAWARE OF THEM AT THAT TIME.

Q. DID YOU SUPPLY THE PATENT OFFICE WITH A COPY OF THE TWO HONG ARTICLES YOU SHOWED US YESTERDAY (SIC)?

A. NO, I DON'T BELIEVE SO.

Q. DID YOU SUPPLY THE PATENT OFFICE WITH A COPY OF THE ARTICLE YOU TOLD US ABOUT INVOLVING THE CHANGING OF THE GENE WHERE YOU TESTED THE PRODUCT BY HAVING A PRIMER GO THROUGH A DOUBLE-STRANDED SECTION?

A. NO, I DON'T THINK SO.

Q. DID YOU PROVIDE THE PATENT OFFICE WITH A COPY OF YOUR DOUBLE-STRANDED SEQUENCING ARTICLE?

A. I DON'T -- I'M NOT SURE, BUT I DON'T THINK SO.
Q. DID YOU PROVIDE THE PATENT OFFICE WITH ANY OF THE THINGS YOU TOLD US YESTERDAY (SIC) IN YOUR EXAMINATION WERE -- WERE RELEVANT TO THESE PATENTS?
A. OH, I'M JUST -- I WAS TRYING TO EXPLAIN THAT THOSE ARE THE THINGS THAT ONE KNEW IN 1984. THOSE ARE --
Q. AND --
A. ONE OF ORDINARY SKILL KNEW THAT STUFF.
Q. DID YOU PROVIDE THE PATENT OFFICE WITH ANY OF THOSE THINGS IN FULFILLMENT OF YOUR OBLIGATION TO PROVIDE MATERIAL INFORMATION?
A. I DON'T KNOW THAT ANY OF THOSE THINGS ARE ANY MORE MATERIAL THAN -- THAN -- IT'S JUST A BODY OF KNOWLEDGE THAT ONE WOULD HAVE HAD AT THAT TIME.
Q. WELL, COULD YOU LOOK THROUGH THIS PATENT APPLICATION, SIR, AND -- AND . . . CONFIRM FOR ME THAT NONE OF THOSE ITEMS WAS PROVIDED TO THE PATENT OFFICE.
A. (WITNESS EXAMINES DOCUMENT.)
AS I SAID, THE SAIKI ARTICLE WAS PROVIDED, WHICH DEMONSTRATED AMPLIFICATION ON DOUBLE-STRANDED DNA TEMPLATES WITH TWO PRIMERS.
Q. NOW, AS TO THAT, YOU ACTUALLY PROVIDED THE PATENT OFFICE WITH A DESCRIPTION OF IT, AND YOU SAID THAT:
"RECENTLY, IT WAS SHOWN THAT SMALL AMOUNTS OF DNA SAMPLES, UNDETECTABLE WITH STANDARD NUCLEIC ACID

HYBRIDIZATION METHODS, CAN BE SPECIFICALLY DETECTED AFTER AMPLIFICATION."

NOW, WHAT DID YOU MEAN BY THE PHRASE THAT "UNDETECTABLE WITH STANDARD NUCLEIC ACID HYBRIDIZATION METHODS"?

A. WELL, I DON'T REMEMBER THE EXACT AMOUNT OF TEMPLATE THAT WAS BEING ANALYZED IN THAT EXPERIMENT, BUT WE HAD SHOWN THAT HYBRIDIZATIONS HAD A SENSITIVITY DOWN TO AROUND HALF A MICROGRAM OF HUMAN DNA, AND I BELIEVE THEY WERE DETECTING SEQUENCES IN LESS THAN THAT AMOUNT IN THE ANALYSIS THEY WERE DOING. SO THAT'S WHAT I MEANT BY "UNDETECTABLE."

Q. SO YOU WERE USING THESE HYBRIDIZATION METHODS THAT YOU DESCRIBED TO MR. FIGG EARLIER THIS MORNING, AND YOU GOT A CERTAIN ABILITY TO DETECT, A CERTAIN LEVEL OF DETECTIONABILITY?

A. THAT'S CORRECT.

Q. AND YOU SAY HERE THAT PCR INCREASED THAT LEVEL OF DETECTIONABILITY?

A. IT'S AN AMPLIFICATION PROCEDURE, SO BY AMPLIFYING, YOU CAN GET MORE SIGNAL FROM A SMALL AMOUNT OF STARTING DNA.

Q. NOW, YOU TOLD US THIS MORNING THERE ALREADY WERE AMPLIFICATION PROCEDURES.

A. THAT'S CORRECT.

Q. DID PCR MAKE IT SO YOU COULD DETECT THINGS THAT COULDN'T BE DETECTED THROUGH THOSE OTHER AMPLIFICATION PROCEDURES YOU DESCRIBED THIS MORNING?

A. NOT NECESSARILY. IT DEPENDS HOW YOU . . . I DON'T -- IF YOU

WANT TO LOOK AT HUMAN DNA, THOSE AMPLIFICATION PROCEDURES WERE CUMBERSOME BUT THEY WERE POSSIBLE. YOU COULD CLONE A GENE, FOR EXAMPLE.

Q. WELL, YOU -- YOU WROTE THIS IN MARCH 1988. NOW, ALL THOSE THINGS YOU WENT THROUGH WITH MR. FIGG HAD ALREADY BEEN PUBLISHED; ISN'T THAT RIGHT?

A. YES, THAT'S CORRECT.

Q. AND YOU, OF COURSE, WERE QUITE FAMILIAR WITH THIS DETECTION LITERATURE. IT WAS -- IT WAS THE CORE OF YOUR WORK, AS YOU EXPLAINED.

A. THAT'S TRUE.

Q. AND YOU SAID TO THE PATENT OFFICE THAT THE PCR METHOD MADE IT POSSIBLE TO DETECT THINGS THAT PRIOR TO THAT TIME WERE UNDETECTABLE.

A. WELL, THE CONTEXT OF THAT SENTENCE MEANT THAT IF YOU WANTED TO STUDY A SAMPLE WHICH CONTAINED A SMALL AMOUNT OF DNA, THE PCR METHOD ALLOWED YOU TO AMPLIFY THE SEQUENCES AND DETECT THEM. THEY WOULDN'T HAVE BEEN DETECTABLE OTHERWISE. BUT, OF COURSE, YOU COULD HAVE CLONED THEM, BUT IT WOULD HAVE BEEN TERRIBLY INCONVENIENT AT THE TIME. TIME-CONSUMING, I GUESS.

Q. I DON'T KNOW WHAT THE IMPORT IS OF YOUR COMMENT THAT YOU COULD HAVE CLONED THEM. THAT DOESN'T -- THAT DOESN'T MAKE UNTRUE WHAT YOU SAID HERE, WHICH IS, WITHOUT PCR, THESE THINGS ARE UNDETECTABLE.

A. WELL, YOU MUST ALSO UNDERSTAND THE SPECIFICATION BASICALLY

WAS PROBABLY DERIVED MORE OR LESS FROM OUR PUBLICATION. THIS . . . AND WE'RE SPEAKING TO AN AUDIENCE OF OUR PEERS. THEY WOULD HAVE UNDERSTOOD WHAT I MEANT THERE.

Q. WHAT -- WHAT DOES "UNDETECTABLE WITH STANDARD NUCLEIC ACID HYBRIDIZATION METHODS" MEAN?

A. IT MEANS THAT THE DNA YOU STARTED WITH -- IN THE DNA YOU STARTED WITH, YOU WOULD NOT HAVE BEEN ABLE TO DETECT THAT SEQUENCE IN THAT DNA WITHOUT . . . WITH STANDARD HYBRIDIZATION METHODS.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) DID YOU ATTEND A CONFERENCE AT COLD SPRING HARBOR IN JUNE 1986?

A. I BELIEVE I DID.

Q. AND DID THAT CONFERENCE RESULT IN THE PUBLICATION OF A LARGE COMPENDIUM OF VARIOUS PRESENTATIONS THAT WERE MADE?

A. YES, I BELIEVE IT DID.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) LET ME PROVIDE YOU WITH BOTH THE ORIGINAL OF THIS FOR YOUR CONVENIENCE AND THE EXHIBIT, WHICH IS A COPY, THAT WE'VE MARKED AS B-192.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, AT THE POINT WHERE I'VE GOT THE FIRST RED FLAG THERE, THERE'S A DESCRIPTION OF A PORTION OF THE PROGRAM; IS THAT RIGHT?

A. (WITNESS EXAMINES PAGE OF BOOK.)

"GENETIC DIAGNOSIS," I GUESS.

Q. IS THERE A PAGE NUMBER ON THAT PAGE IN THAT COPY?

A. XVIII, SO . . . 18. ROMAN 18.

Q. AND THERE UNDER "GENETIC DIAGNOSIS," THERE'S -- THERE'S A LIST OF THE SPEAKERS WHO WERE AT THAT PROGRAM?

A. YES, THAT'S TRUE.

Q. AND YOU WERE THE FIRST SPEAKER?

A. YES, I BELIEVE I WAS.

Q. AND DR. MULLIS WAS THE NEXT SPEAKER.

A. YES, HE . . .

Q. AND AT THAT SPEECH, HE LAID OUT THE WORK HE HAD DONE OVER THE LAST FEW YEARS DEVELOPING PCR.

(PAUSE IN PROCEEDINGS)

THE WITNESS: THAT'S THE TITLE OF HIS TALK, YES. "ENZYMATIC AMPLIFICATION OF DNA IN VITRO TO POLYMERASE CHAIN REACTION."

Q. (BY MR. PASAHOW) WELL, YOU ATTENDED THE PROGRAM.

A. WELL, THIS WAS FOUR YEARS AGO? I DON'T RECALL EXACTLY WHAT THE CONTENT OF HIS SEMINAR WAS.

Q. YOU -- YOU DO RECALL THAT BOTH OF YOU WERE ON THIS PROGRAM.

A. YES, I DO RECALL. WELL, I -- I RECALL THAT I WAS ON THIS PROGRAM. IT SAYS DR. MULLIS WAS ON THIS PROGRAM, TOO. I DON'T RECALL EXACTLY IF THAT WAS THE SEMINAR OF DR. MULLIS I HEARD.

Q. YOU DID HEAR A SEMINAR BY DR. MULLIS AT ABOUT THIS TIME?

A. I'VE HEARD SEMINARS BY DR. MULLIS. I DON'T KNOW IF I HEARD

ONE IN 1986 OR NOT, BUT . . . BUT SINCE I WAS AT THAT PROGRAM, I IMAGINE I DID.

I MEAN, I'M NOT TRYING TO EVADE THE QUESTION. I JUST -- I DON'T TOTALLY RECALL. I WAS ONLY AT THAT MEETING FOR ONE DAY, SO . . .

Q. PRESUMABLY THE DAY YOU AND MR. -- DR. MULLIS SPOKE?

A. WELL, I SPOKE AT THE MEETING SO I OBVIOUSLY WAS THERE THAT DAY.

MR. FIGG: YOUR HONOR, MR. PASAHOW'S QUESTIONS ARE ASSUMING SOMETHING NOT IN EVIDENCE, AND THAT IS THAT THE ORDER OF THE PRESENTATIONS OF THE PROGRAM FOLLOWED THE ORDER WHICH THE ARTICLES ARE LISTED IN THIS BOOK. I DON'T THINK THAT'S BEEN ESTABLISHED.

THE COURT: I DON'T KNOW THAT HE HAS TO ESTABLISH THAT IN ORDER TO ESTABLISH WHAT HE'S ASKING HIM.

MR. FIGG: WELL, I --

THE COURT: YOU MAY PURSUE THE LINE OF QUESTIONING.

Q. (BY MR. PASAHOW) NOW, HOW DID YOU HAPPEN TO BE AT THIS MEETING? WERE YOU INVITED BY SOMEONE TO SPEAK?

A. THERE WAS AN ORGANIZATIONAL COMMITTEE -- I DON'T KNOW WHO IT WAS -- AND I WAS INVITED, YES.

Q. WAS THAT INVITATION FROM DR. WATSON?

A. I DON'T REMEMBER IF DR. WATSON INVITED ME HIMSELF. DR. WATSON'S A CENTRAL FIGURE AT COLD SPRING HARBOR OBVIOUSLY, BUT . . .

HE COULD HAVE INVITED ME, YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) YOU APPLIED FOR YOUR FIRST PATENT INVOLVING PCR AFTER THE TIME OF THIS PROGRAM; IS THAT CORRECT?

(PAUSE IN PROCEEDINGS)

THE WITNESS: (WITNESS EXAMINES DOCUMENT.)

I GUESS IT WAS FILED AFTER THAT TIME, YES.

Q. (BY MR. PASAHOW) NOW, SIR, HAVE YOU EVER DONE A PCR REACTION YOURSELF?

A. I HAVE NEVER . . . ASSEMBLED A PCR REACTION, BUT I'VE DONE PRIMER EXTENSIONS, AND I DIRECT PEOPLE IN MY LABORATORY TO DO THEM.

Q. WHAT TYPE OF PEOPLE IN YOUR LABORATORY DO PCR REACTIONS? WHAT ARE -- WHAT ARE THEIR POSITIONS?

A. THEY'RE EITHER TECHNICIANS, OR POST-DOCTORAL FELLOWS, OR VISITING SCIENTISTS.

Q. IS IT CORRECT THAT MOST PCR REACTIONS IN YOUR LABORATORY ARE DONE BY TECHNICIANS?

A. I DON'T THINK THAT'S CORRECT.

Q. WHAT IS THE TRAINING OF THE TECHNICIANS WHO DO THE PCR REACTIONS?

A. WELL, ACTUALLY, AT THE MOMENT, THE PERSON WHO'S DOING IT IN MY LABORATORY -- I DON'T KNOW THAT A TECHNICIAN'S EVER DONE ONE IN MY LABORATORY ACTUALLY. I HAVE TO THINK.

I HAVE A PERSON IN MY LABORATORY WHO'S A VISITING

SCIENTIST FROM ITALY. HE HAS THE TRAINING OF THE -- ACTUALLY, HIS TRAINING WAS ORIGINALLY IN ARGENTINA, WHICH IS AN EQUIVALENT OF A PH.D., AND HAS WORKED MANY YEARS IN A LABORATORY AND IS IN MY LABORATORY. HE DOESN'T HAVE A PH.D., BUT HE'S WORKING AS A VISITING SCIENTIST, SO HE HAS MANY YEARS OF TRAINING, THE ONE WHO DOES THE MOST.

Q. YOU CAN'T RECALL A TECHNICIAN EVER DOING A PCR REACTION IN YOUR LABORATORY?

A. WELL, I'M JUST TRYING TO THINK.

OKAY. I HAVE A RECENT TECHNICIAN WHO HAS A MASTER'S DEGREE, YEAH.

Q. AND DOES THAT PERSON DO PCR REACTION?

A. YES, HE DOES.

Q. AND WHEN THE -- THE KIND OF CHANGING OF THE PARTS OF THE REACTION HAVE TO BE DONE THAT YOU DESCRIBED TO MR. FIGG, THIS PERSON WORKS THAT OUT?

A. WELL, USUALLY I WORK THAT OUT.

Q. HOW MANY TIMES HAVE YOU DONE THAT, WHERE YOU'VE GOTTEN INVOLVED AND HAD TO CHANGE THE CONDITIONS OF A PCR REACTION TO MAKE IT WORK?

A. ALMOST EVERY DAY.

Q. ALMOST EVERY DAY?

A. WELL, I MEAN, IT'S A -- WE'RE ALWAYS CHANGING THE CONDITIONS BECAUSE IT DOESN'T WORK ONE WAY OR THE OTHER.

Q. IT DOESN'T WORK AT ALL.

A. OH, IT EITHER DOESN'T WORK AT ALL OR GIVES YOU NON-SPECIFIC REACTION. THAT'S THE KIND OF THING.

Q. WELL, LET'S START WITH NON-SPECIFIC REACTION:

WHAT DO YOU MEAN BY THAT?

A. WELL, IF YOU . . . FOR EXAMPLE -- WELL, I THINK WE MUST SAY WHAT WE'RE TALKING ABOUT HERE:

MODERN DAY PCR IS QUITE DIFFERENT THAN THE -- SOME OF THE PROCESSES WE'RE TALKING ABOUT. TODAY, WE USE A THERMOSTABLE ENZYME; WE USE AUTOMATED INSTRUMENTATION; WE GO THROUGH MANY CYCLES.

SO, FOR EXAMPLE, IF YOU CHANGE THE TEMPERATURE OF THE REACTION, YOU WILL HAVE A SITUATION OFTEN WHERE THE GENE WON'T AMPLIFY BUT OTHER THINGS WILL THAT HAVE NOTHING TO DO WITH THE GENE. OR YOU WILL AMPLIFY THE GENE AND YOU'LL AMPLIFY MANY OTHER THINGS WHICH HAVE NOTHING TO DO WITH THAT GENE. THAT KIND OF PROBLEM.

Q. SO THE PCR REACTION DOES THE AMPLIFICATION. IT'S JUST IT AMPLIFIES PARTS OF WHAT'S IN THAT TUBE THAT YOU DON'T WANT.

A. IT AMPLIFIES NON-SPECIFIC SEQUENCES.

Q. WELL, IT AMPLIFIES A SPECIFIC SEQUENCE. IT'S JUST NOT THE SPECIFIC SEQUENCE YOU WANT.

A. OH, I NEVER ANALYZED THE SEQUENCES OF THESE PRODUCTS OTHER THAN BY HYBRIDIZATION --

Q. I SEE.

A. -- AND THEY DON'T HAVE THE SEQUENCE I'VE DESIRED.

BUT IF YOU'RE GETTING A -- THE HUMAN GENOME HAS ONE GENE, AND YOU GET 10 OR 20 BANDS ON THE GEL, IT'S NON-SPECIFIC.

Q. IT WOULDN'T BE UNUSUAL FOR THERE TO BE 10 TO 20 SEQUENCES IN HUMAN DNA THAT HAD EXACTLY THE SEQUENCE OF THE TWO PRIMERS THAT YOU CHOSE; ISN'T THAT RIGHT?

A. IT WOULD BE UNUSUAL, YES.

Q. IT WOULD BE UNUSUAL.

A. YES.

Q. WOULD IT BE UNUSUAL FOR THE HUMAN DNA TO HAVE SEQUENCES THAT WERE VERY CLOSE TO THE PRIMERS YOU CHOSE?

A. IT DEPENDS ON THE LENGTH OF THE PRIMERS, BUT IT WOULD BE UNUSUAL IF THE PRIMER WERE OF ANY LENGTH AT ALL.

Q. WELL, WHEN YOU GET THESE OTHER BANDS, WHAT DO YOU THINK CAUSES THEM?

A. NON-SPECIFIC PRIMING.

Q. NON-SPECIFIC PRIMING BY OTHER PRIMERS?

A. IT -- YOU CAN'T -- I HAVEN'T ANALYZED THEM IN THAT WAY.

Q. I SEE. SO YOU DON'T KNOW WHAT IS IN THESE OTHER BANDS?

A. WELL, I'VE ANALYZED THEM BY HYBRIDIZATION. I KNOW THEY CONTAIN PRIMER SEQUENCES, YES.

Q. SO WHAT IS AMPLIFIED DOES CONTAIN THE PRIMER SEQUENCE.

A. YEAH. SOME OF WHAT IS AMPLIFIED CONTAINS THE PRIMER SEQUENCE, YES.

Q. WELL, HAVE YOU EVER HAD A PRODUCT AMPLIFIED WHICH -- TO WHICH A PRIMER WOULD NOT BIND IF YOU USED IT AS A PROBE?

A. I'M SORRY. COULD YOU REPEAT THE QUESTION?

Q. YES.

DID YOU EVER HAVE A SEQUENCE AMPLIFIED WHICH WAS NOT COMPLEMENTARY TO THE PRIMER OR SUBSTANTIALLY COMPLEMENTARY TO THE PRIMER?

A. I'VE NEVER LOOKED AT IT THAT WAY. I'VE ONLY LOOKED AT THE TOTAL, AND THERE ARE PRIMER SEQUENCES IN THE AMPLIFIED PRODUCT.

Q. UH-HUH.

A. THAT'S ALL I KNOW.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, WHEN DID A PCR REACTION FIRST GET DONE IN YOUR LABORATORY?

A. I DON'T KNOW THE EXACT DATE AFTER THE . . . AFTER THE SCIENCE ARTICLE APPEARED.

Q. AFTER THE CETUS SCIENCE ARTICLE APPEARED --

A. YES.

Q. -- IN DECEMBER 1985?

A. YES.

Q. WAS IT AFTER YOU ATTENDED THIS CONFERENCE WITH DR. MULLIS IN JUNE 1986?

A. I DON'T RECALL. PROBABLY NOT. PROBABLY BEFORE THAT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) DID YOU HAVE SOME INVOLVEMENT IN -- IN THAT FIRST PCR REACTION THAT WAS DONE IN YOUR LABORATORY?

A. THE . . . WHAT WE WERE DOING, WE WERE TEACHING GRADUATE

STUDENTS, AND THESE STUDENTS WANTED TO DO . . . PCR'S, SO WE WERE TEACHING THEM, SEVERAL OF US, DR. ROSSI, DR. ZAIA, AND MYSELF.

Q. NOW, BEFORE THE TIME OF THE CETUS ARTICLE IN DECEMBER 1985, YOU HAD NEVER USED THE PCR PROCESS?

A. I HAD JUST USED THE PRIMER EXTENSION REACTIONS, AS I'VE DISCUSSED.

Q. YOU HAD NEVER USED THE PRIMER EXTENSION REACTIONS IN A WAY WHICH WAS PCR AS DEFINED BY THE PATENTS.

A. I NEVER USED PRIMER EXTENSION REACTIONS TO PERFORM AN AMPLIFICATION, THAT'S CORRECT.

Q. WHY NOT?

A. BECAUSE I HAD NOT READ THE KHORANA PRIOR ART, UNFORTUNATELY.

Q. WELL, YOU WERE HERE WHEN DR. KORNBERG TESTIFIED.

A. UH-HUH.

Q. AND YOU HEARD DR. KORNBERG TELL US THAT THE ORDINARY PRINCIPLES OF PRIMER EXTENSION PREDICT PCR.

A. THAT'S . . . I GUESS THAT'S WHAT HE SAID, YES.

Q. DO YOU RECALL THAT HE TOLD US THAT ANYONE FAMILIAR WITH THE PRIMER EXTENSION REACTION IN THE LATE 1960'S AFTER HE DISCLOSED HIS WORK COULD HAVE PREDICTED PCR?

A. WELL, DR. KHORANA PUBLISHED IT, OF COURSE, YEAH, IN 1971 --

Q. YES, SIR.

A. -- SO --

Q. THIS -- WE WERE TALKING ABOUT BACK IN THE 1960'S WITH DR.

KORNBERG.

A. UH-HUH.

Q. AND HE VERY CLEARLY TOLD US THAT ANYONE FAMILIAR WITH THE PRIMER EXTENSION REACTION, AS A -- AS HIS WORK DISCLOSED IT IN THE LATE 1960'S, COULD HAVE PREDICTED PCR.

AND HE ANSWERED: "I WOULDN'T SAY ANYONE. ONE WOULD HAVE TO KNOW THIS FIELD AND BE VERY FAMILIAR WITH IT, YES."

A. (NODDING HEAD.)

Q. NOW, YOU KNEW THIS FIELD.

A. UH-HUH.

Q. IS THAT CORRECT?

A. RIGHT.

Q. AND YOU WERE VERY FAMILIAR WITH PRIMER EXTENSION REACTIONS.

A. THAT'S CORRECT.

Q. NOW, THIS WORK PREDICTED PCR, ACCORDING TO DR. KORNBERG. WERE YOU --

A. WHICH WORK ARE YOU TALKING ABOUT?

Q. THE WORK THAT DR. KORNBERG DID --

A. YES.

Q. -- WITH PRIMER EXTENSION REACTIONS IN THE 1960'S.

A. IT CERTAINLY TAUGHT PRIMER EXTENSION.

Q. YES.

A. I HAVE USED PRIMER EXTENSION EXTENSIVELY, AS I'VE TESTIFIED.

Q. WOULD YOU AGREE THOSE PRINCIPLES OF PRIMER EXTENSION

REACTION PREDICTED PCR SO ANYONE FAMILIAR WITH THE PROCESS COULD HAVE DONE IT?

A. WELL, I FEEL THAT THE KLEPPE, PANET, AND THE KHORANA GRANT APPLICATION WOULD HAVE GIVEN THE NECESSARY INSIGHT.

Q. I UNDERSTAND YOU BELIEVE THAT, SIR.

A. UH-HUH.

Q. THE QUESTION WAS DIFFERENT, THOUGH, AND THAT WAS:

DO YOU AGREE WITH DR. KORNBERG THAT ANYONE FAMILIAR WITH THE PRIMER EXTENSION REACTION AS IT WAS KNOWN IN THE LATE 1960'S COULD HAVE DONE PCR?

A. I THINK THEY COULD HAVE DONE PCR.

Q. AND YOU, OF COURSE, WERE FAMILIAR WITH EVERYTHING THAT WAS KNOWN ABOUT PRIMER EXTENSION REACTIONS IN THE LATE 1960'S.

A. THAT'S TRUE.

Q. AND YOU DIDN'T DO PCR.

A. NO, I DID NOT.

Q. WOULD PCR HAVE BEEN HELPFUL TO YOU IN YOUR WORK BEFORE DECEMBER 1985?

A. IT WOULD NOT HAVE BEEN. I MEAN, I WAS DEDICATED TO DOING A CERTAIN SERIES OF EXPERIMENTS THAT DEALT MAINLY WITH HYBRIDIZATIONS AND SPECIFIC -- SPECIFICITY OF HYBRIDIZATIONS AND DETECTING HUMAN GENETIC DISEASES, SO I DID NOT . . . THINK IT NECESSARY TO AMPLIFY MY TEMPLATE.

Q. YOU DID A SERIES OF EXPERIMENTS IN WHICH YOU WERE TRYING TO IMPROVE THE SENSITIVITY OF YOUR ABILITY TO DETECT THE HEMO --

A. YES.
Q. -- HEMOGLOBIN SICKLE CELL GENE; IS THAT RIGHT?
A. THAT'S TRUE.
Q. AND PCR IS THE MOST DRAMATIC IMPROVEMENT IN SENSITIVITY THAT CAME ALONG; ISN'T IT?
A. WELL, OUR WORK WAS, BEFORE THAT, THE MOST DRAMATIC IMPROVEMENT SENSITIVITY, I WOULD IMAGINE, SO I -- I WAS TRYING TO IMPROVE SENSITIVITY BY IMPROVING THE SENSITIVITY OF THE -- OF THE PROBE. PCR ATTEMPTED TO DO IT BY AMPLIFYING THE TEMPLATE.
Q. AND THE WORK YOU'RE REFERRING TO IS THE CONNER ARTICLE YOU DISCUSSED WITH MR. FIGG?
A. NO. THE -- THERE'S OTHER ARTICLES.
(PAUSE IN PROCEEDINGS)
Q. (BY MR. PASAHOW) LET ME SHOW YOU, SIR, AN ARTICLE THAT WE HAVE MARKED AS EXHIBIT B-151.
A. (WITNESS EXAMINES DOCUMENT.)
Q. ARE YOU FAMILIAR WITH THAT ARTICLE?
A. I AM.
Q. ARE YOU AN AUTHOR OF IT?
A. I AM.
Q. WHEN DID YOU WRITE THAT ARTICLE?
A. 1989.
Q. 1989. THAT --
A. IT WAS PUBLISHED IN 1989.
Q. AND IS IT TRUE THAT, AT THE TIME YOU WROTE THIS ARTICLE, IT

WAS YOUR BELIEF THAT THE PROBLEMS THAT HAD BEEN INVOLVED IN THE PRIOR ART OF DIAGNOSING GENETIC DISEASES WITH PROBES WERE A COMBINATION OF SENSITIVITY AND SPECIFIC -- SPECIFICITY?

A. YES.

Q. AND WAS IT YOUR BELIEF THAT, ALTHOUGH VARIOUS IDEAS HAD BEEN PUT FORWARD TO IMPROVE SENSITIVITY, NONE WAS MORE DRAMATIC THAN THE POLYMERASE CHAIN REACTION?

A. YES, THE POLYMERASE CHAIN REACTION DEFINITELY IMPROVED SENSITIVITY.

Q. AND IT IMPROVED IT DRAMATICALLY.

A. YES.

Q. AND, OF COURSE, THAT'S WHAT YOU WROTE HERE IN THE ARTICLE.

A. YEAH, OF COURSE.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, THIS DRAMATIC IMPROVEMENT IN THE SENSITIVITY OF THE DETECTION PROCESS THAT YOU WERE TRYING TO DO, DON'T YOU THINK THAT WOULD HAVE BEEN USEFUL TO YOU BACK BEFORE 1989?

A. PROBABLY WOULD HAVE BEEN, YES. BEFORE 1989.

Q. BEFORE 1985?

A. IF WE HAD THOUGHT UP -- THOUGHT OF THE AMPLIFYING THE TEMPLATE, IF WE'D KNOWN ABOUT THE KLEPPE ARTICLE, WE MAY VERY WELL HAVE WORKED ON AMPLIFYING THE TEMPLATE. BUT OUR WORK WAS DEDICATED TOWARDS AMPLIFYING THE SIGNAL FROM THE PROBE.

Q. WELL, YOU CHANGED THAT WORK RATHER QUICKLY AFTER YOU LEARNED

OF CETUS' PUBLICATION; ISN'T THAT RIGHT?

A. WELL, THAT'S NOT EXACTLY TRUE. WE DID THE WORK THAT WE'VE BEEN DISCUSSING WITH RESPECT TO THIS AIDS TEST. THAT INVOLVED USING THE KLENOW DNA POLYMERASE WE'VE BEEN DISCUSSING.

BUT MY LABORATORY DIDN'T PURSUE THAT PARTICULARLY BEYOND THAT. THIS WORK WAS DONE ACTUALLY MORE IN DR. ROSSI'S LAB, BECAUSE I FOUND IT MORE CONVENIENT TO CONTINUE ALONG THESE LINES UNTIL IT BECAME POSSIBLE TO DO AMPLIFICATION AUTOMATICALLY.

Q. WELL, HOW MANY PATENTS HAVE YOU APPLIED FOR THAT -- THAT HAVE AS THEIR BASIS THE PCR PROCESS?

A. I DON'T KNOW. I DON'T KNOW.

Q. CERTAINLY MORE THAN THAT ONE.

A. PROBABLY, YEAH. THERE ARE OTHERS, YES.

Q. NOW, THIS DRAMATIC IMPROVEMENT IN SENSITIVITY FOR DETECTING SICKLE CELL ANEMIA, THAT WOULD HAVE BEEN USEFUL TO YOU BACK IN 1984.

A. WELL, IT WOULD HAVE BEEN USEFUL TO ME, BUT THIS PAPER DESCRIBES HOW -- OUR STRATEGY FOR DOING THIS DRAMATIC IMPROVEMENT. THIS GOES BEYOND PCR. IT HAS . . . AND PROVIDED OUR OWN WAY OF AMPLIFYING THE SIGNAL BY ANOTHER METHOD BEYOND PCR, WHICH HAD BOTH THE SENSITIVITY AND SPECIFICITY BUILT INTO IT, WHEREAS PCR BASICALLY IMPROVED SENSITIVITY.

SO WE WERE WORKING ON OUR OWN METHODS OF AMPLIFICATION.

Q. IN 1989, YOU WERE.

A. WELL, I DON'T REMEMBER WHEN WE BEGAN THIS WORK. YOU NEVER BEGIN IT THE DAY YOU PUBLISH IT.

Q. WELL, LET'S GO BACK TO 1984:

YOU WEREN'T WORKING ON THIS PROCESS IN 1984.

A. NO.

Q. AND IN 1984, WHY WEREN'T YOU USING PCR TO AMPLIFY YOUR HEMOGLOBIN BEFORE YOU PROBED FOR IT?

A. I DIDN'T KNOW ABOUT THE KHORANA PRIOR ART.

Q. WELL, WE JUST WENT THROUGH THE FACT THAT -- THAT, ACCORDING TO DR. KORNBERG, YOU DON'T NEED THAT THAT ART. ANYONE WHO WAS FAMILIAR WITH THE ORDINARY PRINCIPLES OF PRIMER EXTENSION COULD DO PCR.

A. WELL, THE PRINCIPLES OF PRIMER EXTENSION CERTAINLY ARE IMPORTANT. I THINK THAT THE BASIC CONCEPT OF PCR IS THE TWO PRIMERS ORIENTED APPROPRIATELY ON THE TEMPLATE, WHICH IS TAUGHT BY THE KHORANA PRIOR ART. I THINK IT'S VERY IMPORTANT.

Q. WELL, YOU SAY YOU WEREN'T AWARE OF THE KHORANA PRIOR ART IN 1984?

A. (SHAKING HEAD.) NO, I WAS NOT.

Q. YOU DID A RATHER COMPREHENSIVE REVIEW OF THE ART DEALING WITH SYNTHETIC -- SYNTHESIS AND USE OF SYNTHETIC OLIGONUCLEOTIDES IN 1984?

A. WELL, THREE OF US DID, YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) LET ME SHOW YOU WHAT WE'VE MARKED AS

EXHIBIT B-190.

YOU'RE A CO-AUTHOR OF THAT ARTICLE?

A. I AM.

Q. WHAT IS THIS ARTICLE?

A. IT WAS A REVIEW ON THE SYNTHESIS AND USE OF SYNTHETIC OLIGONUCLEOTIDES BY KEIICHI ITAKURA, JOHN ROSSI, AND MYSELF.

Q. NOW, DR. ITAKURA, HE CERTAINLY IS SOMEONE OF FAR GREATER ABILITY THAN ORDINARY SKILL IN THE ART.

A. IN WHAT AREA?

Q. IN -- IN --

A. IN DNA SYNTHESIS, THAT'S TRUE. HE WAS A PIONEER IN DNA SYNTHESIS.

Q. AND DR. ROSSI, HE WAS SOMEONE OF FAR GREATER THAN ORDINARY SKILL IN THE ART.

A. AT THE TIME, I DON'T KNOW WHAT DR. ROSSI'S POSITION WAS. HE . . . WAS ORIGINALLY A POST-DOC WITH DR. ITAKURA AND JOINED OUR FACULTY. PROBABLY, HE HAD JOINED THE FACULTY BY THE TIME THIS WAS WRITTEN.

Q. AND SO WOULD YOU CONSIDER HIM TO BE ORDINARILY SKILLED AT THE TIME?

A. WELL, HE'S BEYOND THE . . . HE'S HAD MORE TRAINING THAN -- THAN THE PERSON WE WERE TALKING ABOUT.

Q. WELL, THE QUESTION, SIR, IS: AT THE TIME THIS ARTICLE WAS WRITTEN, IN 1984, DID YOU BELIEVE DR. ROSSI TO BE OF ORDINARY SKILL IN THE ART?

A. WELL, DR. ROSSI HAD -- WAS BEYOND ORDINARY SKILL IN THE GENE CONSTRUCTION EXPERIMENTS AND CLONING EXPERIMENTS HE WAS PARTICIPATING IN, TRUE.

Q. DO YOU DISTINGUISH THAT FROM -- FROM THE ART THAT YOU THINK IS RELEVANT TO SOMEONE WHO WOULD HAVE USED PCR?

A. HE WAS FAMILIAR WITH PRIMER EXTENSIONS AND . . .

(NODDING HEAD.)

HE USED PRIMER EXTENSIONS.

Q. AND, OF COURSE --

A. SO THAT HE -- YEAH. I DIDN'T ANSWER THE QUESTION.

HE IS IN THAT SAME GENERAL FIELD THAT WE'VE BEEN TALKING ABOUT.

Q. AND, OF COURSE, IN 1984, YOU WERE MORE THAN ORDINARILY SKILLED IN -- IN THIS ART.

A. THAT'S TRUE.

Q. NOW, IN THIS ARTICLE, YOU WANTED TO EXPLAIN HOW THESE SYNTHETIC PIECES OF DNA THAT ARE USED AS PRIMERS AND PROBES WERE MADE?

A. THE POINT OF THE ARTICLE WAS TO TELL SOMEBODY HOW TO MAKE DNA AND THEN HOW TO USE DNA.

Q. AND BY DNA, YOU MEAN THESE SHORT PIECES OF SYNTHETIC DNA THAT WERE USED AS PRIMERS AND PROBES.

A. THAT'S CORRECT.

Q. AND, OF COURSE, ONE OF THE WAYS ONE USES THESE SHORT PIECES OF SYNTHETIC DNA IS IN PCR.

A. THAT'S CORRECT.

Q. WHAT DOES THIS ARTICLE SAY ABOUT PCR?

A. THIS ARTICLE ONLY DESCRIBES -- WELL, I DON'T KNOW EXACTLY. I IMAGINE IT DESCRIBES DR. ROSSI'S WORK, IT DESCRIBES MY WORK ON PROBES, SO IT DESCRIBES THE PRIMER EXTENSION PROCESS.

Q. WHAT WAS DR. ROSSI'S WORK?

A. DR. ROSSI'S WORK WAS TO -- WELL, HE DID SEVERAL THINGS. HE CLONED A SYNTHETIC BACTERIAL PROMOTER.

Q. WHEN YOU SAY THAT THIS ARTICLE DESCRIBED DR. ROSSI'S WORK, WHAT -- WHAT WORK OF HIS DID IT DESCRIBE?

A. WELL, I MEAN, IF YOU LOOK AT FIGURE -- LET'S FOCUS ON FIGURE 4, FOR EXAMPLE. DR. ROSSI DESCRIBED GENE SYNTHESIS BY PRIMER EXTENSION REACTIONS. HE DESCRIBED -- I BELIEVE HE WAS DESCRIBING IN VITRO MUTAGENESIS PROCEDURES AS WELL IN HERE --

Q. THIS IS --

A. -- SYNTHETIC DNA -- SPECIFICALLY TO GENESIS. HE WAS DESCRIBING THOSE PROCESSES, TOO, WHICH ALSO DESCRIBED PRIMER EXTENSION REACTION.

Q. NOW, BY FIGURE 4, YOU'RE REFERRING TO THE FIGURE THAT INCLUDES WHAT I'VE NOW GOT ON THE TELEVISION PROJECTOR HERE?

A. YES, THAT'S CORRECT.

Q. NOW, THIS -- THIS DRAWING HERE, IS THAT A PRIMER EXTENSION REACTION?

A. YES, IT IS.

Q. AND WHAT'S GOING TO HAPPEN IS, EACH OF THESE TWO PIECES OF

DNA HERE ARE SET UP AND THEY OVERLAP SLIGHTLY?

A. THAT'S CORRECT.

Q. AND DR. ROSSI ADDED POLYMERASE AND CAUSED THEM TO THEN EXTEND TO THE ENDS?

A. THAT'S CORRECT.

Q. AND HE HAS TWO PIECES HERE. HE THEN WENT THROUGH THE PROCESS OF PUTTING THEM TOGETHER?

A. THAT'S CORRECT.

Q. HOW DID HE PUT THEM TOGETHER?

A. HE PUT THEM TOGETHER BY LIGATION.

Q. CAN YOU EXPLAIN WHAT THAT MEANS.

A. HE PUT THEM TOGETHER BY -- THERE'S ANOTHER ENZYME CALLED DNA LIGASE WHICH CREATES THE JOINTS BETWEEN BUILDING BLOCKS IF THOSE BUILDING BLOCKS CAN BE BROUGHT TOGETHER AND -- AND CAUSES THEM TO BE -- TO BE JOINED. AND BY BRINGING THOSE TOGETHER WITH WHAT'S CALLED BLUNT END, BLUNT ENDS TOGETHER, THEY CAN BE JOINED AT THAT END.

Q. AND THEN WHEN HE GOT ALL DONE WITH THAT, DR. ROSSI PUT THESE INTO A BACTERIA AND CAUSED THE BACTERIA TO DIVIDE?

A. THAT'S CORRECT.

Q. AND AFTER THE BACTERIA HAD DIVIDED MANY TIMES, HE BROKE IT OPEN AND TOOK THE DNA OUT?

A. THAT'S CORRECT.

Q. AND THEN AFTER HE GOT THE DNA OUT, HE -- HE USED SOME SPECIAL ENZYMES TO CUT IT SO HIS PIECE WAS CUT?

A. THAT WOULD SEEM LOGICAL. I HAVEN'T READ THIS IN A LONG TIME.

Q. AND THEN HE'D HAVE TO PURIFY OUT THE PIECE HE WANTED FROM ALL THE REST OF THIS STUFF.

A. THAT'S CORRECT.

Q. NOW --

A. THAT'S THE PROCESS OF CLONING, USING THE BACTERIA TO PURIFY YOUR DNA FOR YOU.

Q. USING YOUR BACTERIA TO . . .

A. TO PURIFY THE DNA.

Q. TO --

A. A CLONE IS -- IS . . . RESULTS FROM ONE MOLECULE, SO HE WOULD JOIN THEM, DO THIS PROCESS, PUT THEM INTO THE BACTERIA, AND OBTAIN A SINGLE CLONE WHICH CAME FROM A SINGLE MOLECULE AND GO THROUGH THE PROCESS YOU DESCRIBED.

Q. NOW, WHEN DR. ROSSI IS AT THIS STEP RIGHT AT THE BEGINNING, HE'S ALL SET TO DO PCR, IF HE WANTS; ISN'T HE?

A. NO. IT WOULDN'T MAKE ANY SENSE TO DO PCR THERE.

Q. WHY NOT?

A. WELL, BECAUSE THIS IS A PRIMER EXTENSION REACTION WHICH CONSUMES THE PRIMERS IN THE FIRST STEP.

Q. WELL, THAT'S RIGHT. BUT COULDN'T HE HAVE USED THOSE -- THOSE TWO END PRIMERS AS PRIMERS TO JUST GO AHEAD AND DO A PCR REACTION, THIS PIECE HERE (INDICATING) AND THIS PIECE HERE (INDICATING)?

(PAUSE IN PROCEEDINGS)

THE WITNESS: THAT ASSUMES THAT HE HAS A GENE THAT HE HAS AVAILABILITY OF. I MEAN, THE BEAUTY OF DNA SYNTHESIS IS THAT YOU CAN SYNTHESIZE ANY GENE, AND THAT'S THE WHOLE POINT OF DR. KHORANA'S WORK, DOCTOR ITAKURA'S WORK, AND THIS WORK FROM DR. ROSSI, IS THAT YOU'RE SYNTHESIZING GENES WHICH MAY HAVE NEVER EXISTED BEFORE.

Q. (BY MR. PASAHOW) UH-HUH.

A. THIS IS A STUDY OF THAT PROCESS.

AND THIS PRIMER EXTENSION REACTION -- WELL, YOU'VE SLID IT OFF, BUT . . . SHOULD BE QUANTITATIVE, SHOULD CONSUME THE PRIMERS IN THE FIRST STEP AND, THEREFORE, YOU SHOULD BE ABLE TO JUST JOIN THOSE AND CLONE THEM.

Q. NOW, AFTER YOU JOIN THEM, AND YOU'VE GOT THE WHOLE GENE, CERTAINLY AT THAT POINT, RATHER THAN CLONE IT, YOU COULD HAVE JUST PUT IN YOUR -- YOUR TWO PRIMERS AND DONE A PCR REACTION.

A. YOU COULD HAVE, BUT THAT -- THAT ALSO WOULDN'T HAVE MADE ANY SENSE.

Q. WHY IS THAT?

A. BECAUSE YOU WANT TO GET A CLONE. DNA SYNTHESIS AND PRIMER EXTENSION, AS WE'VE ALREADY HEARD, ARE NOT COMPLETELY ACCURATE. THEY MAKE MISTAKES, FOR EXAMPLE. SO YOU ACTUALLY GET A -- FROM THIS PROCESS, OR A PCR PROCESS, FOR THAT MATTER, A MIXTURE OF MOLECULES.

Q. WELL, WHETHER IT WOULD HAVE MADE SENSE FOR DR. ROSSI'S

PARTICULAR PURPOSE OR NOT, WOULD ANYTHING HAVE STOPPED HIM WHEN HE GOT DOWN TO THIS POINT HERE (INDICATING) AND JOINED THESE TWO TOGETHER FROM TAKING HIS TWO PRIMERS FROM THE TOP AND MAKING ALL HE WANTED OF THIS GENE USING PCR?

A. WELL, YOU'RE PRESUMING A MOTIVATION HERE, BUT, NO, HE COULD HAVE DONE PCR AT THAT POINT.

Q. AND IN YOUR PAPER, YOU DON'T SAY ANYTHING ABOUT USING PCR FOR AMPLIFICATION.

A. NO, WE DON'T.

Q. NOW, IN YOUR PAPER, YOU DO DISCUSS SOME OF THE WORK FROM DR. KHORANA'S LABORATORY; IS THAT RIGHT?

A. YEAH. I THINK -- WELL, OBVIOUSLY, THE WORK THAT WAS IMPORTANT TO SYNTHESIS AND THE WORK THAT WAS IMPORTANT TO THE PRIMER EXTENSION REACTION, THE LIGASE REACTION AND SO ON, YES.

Q. UH-HUH. SO THIS PAPER DOES CONSIDER WORK THAT CAME OUT OF DR. KHORANA'S LABORATORY.

A. THAT'S CORRECT.

Q. AND THAT WAS WORK THAT WAS DONE AT ABOUT THE SAME TIME AS THE ARTICLES YOU'RE TALKING ABOUT IN YOUR TESTIMONY.

A. I IMAGINE SOME OF IT WAS, YES.

(PAUSE IN PROCEEDINGS)

THE WITNESS: I DIDN'T WRITE THOSE SECTIONS.

Q. (BY MR. PASAHOW) UH-HUH. AND THE ARTICLE, OF COURSE, TALKS ABOUT THE USE OF THESE SYNTHETIC SHORT PIECES OF DNA AND PRIMER EXTENSION REACTIONS.

A. THAT'S CORRECT.
Q. BUT IT -- IT NEVER TALKS ABOUT USING THEM IN A PRIMER EXTENSION REACTION WHERE YOU'RE DOING EXPONENTIAL AMPLIFICATION.
A. NO, IT DID NOT.
Q. AND IT DOESN'T TALK ABOUT THEM BECAUSE, WHEN YOU WROTE THIS IN 1984, YOU DIDN'T KNOW ABOUT IT.
A. I DIDN'T --
Q. AND --
A. -- KNOW ABOUT KLEPPE, PANET, AND THE KHORANA GRANT APPLICATION.
Q. AND YOU DIDN'T THINK A PCR BACK THEN BASED UPON THE BASIC PRINCIPLES OF PRIMER EXTENSION REACTIONS LIKE DR. KORNBERG TOLD US COULD HAVE.
A. I WAS VERY WELL ACQUAINTED WITH THE PRIMER EXTENSION REACTIONS --
Q. YES, SIR.
A. -- BUT I WAS NOT USING THEM IN AMPLIFICATION REACTION AS DESCRIBED BY DR. KHORANA, NO.
Q. AND THAT'S BECAUSE IT DIDN'T OCCUR TO YOU THAT YOU COULD DO THAT.
A. I DIDN'T KNOW ABOUT IT, THAT'S TRUE.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, YOU TELL US THAT DR. KLEPPE'S PROCESS RESULTS IN EXPONENTIAL AMPLIFICATION.
A. YES, IT DOES.

Q. IF IT REALLY DID THAT, AND IF IT WERE KNOWN TO YOU IN 1984, IT CERTAINLY WOULD HAVE BEEN VERY USEFUL TO YOU AT THAT TIME.

A. OH, I ALREADY UNDERSTOOD THAT. THAT'S HOW DNA REPLICATION WORKS.

Q. IF YOU HAD AN EXPONENTIAL AMPLIFICATION PROCESS THAT YOU COULD DO IN A TEST TUBE IN 1984, THAT WOULD HAVE BEEN VERY USEFUL TO YOU IN 1984 WHEN YOU WROTE THIS ARTICLE.

A. IT MAY NOT HAVE BEEN, BECAUSE, AS I SAID, WHEN I LEARNED ABOUT THE WORK WITH THE KLENOW POLYMERASE FROM THE -- BY SAIKI AND OTHERS, THAT PROCESS, WE ATTEMPTED IT, BUT IT DIDN'T BECOME VERY USEFUL UNTIL, YOU KNOW, DRAMATIC NUMBERS OF OTHER PROTOCOLS AND SO ON HAD BEEN -- FOR EXAMPLE, THE INTRODUCTION OF THERMOSTABLE ENZYMES.

SO THAT -- IF THE THERMOSTABLE ENZYME AND THE AUTOMATED INSTRUMENTATION HAD BEEN AVAILABLE TO ME IN '84 IT WOULD HAVE BEEN VERY USEFUL, YES.

Q. THE -- YOU TOLD MR. FIGG THAT THE THERMOSTABLE ENZYME WAS KNOWN AT THE TIME THAT --

A. IT WAS KNOWN, BUT I WAS NOT IN A POSITION TO PURIFY IT. I DON'T KNOW THAT IT WAS COMMERCIALLY AVAILABLE.

Q. SO THE THERMOSTABLE ENZYME WAS CERTAINLY AVAILABLE IN THE ART.

A. THE -- YEAH, THE . . . AS I UNDERSTOOD IT.

Q. YES.

AND -- AND PCR WAS AVAILABLE STARTING IN 1985, AND YOU

STARTED USING IT WITHOUT A THERMOSTABLE ENZYME.

A. YES, I DID.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) LET ME SHOW YOU, SIR, THE PATENT WE HAVE MARKED AS EXHIBIT B-189. IT'S SERIAL NUMBER 283,142.

A. (WITNESS EXAMINES DOCUMENT.) YES.

Q. YOU'RE FAMILIAR WITH THIS PATENT?

A. I AM.

Q. AGAIN, YOU ARE ONE OF THE INVENTORS?

A. I AM.

Q. WHEN DID YOU SIGN THE OATH IN REGARD TO THIS PATENT?

A. JANUARY 20TH, 1989.

Q. 1989?

A. YES.

Q. WHAT DOES THIS PATENT CONCERN?

A. WELL, THIS PATENT DESCRIBES A PROCESS WHICH IS DIFFERENT THAN PCR. IT'S A PROCESS WHERE PCR DOESN'T WORK. AND WHEN PCR DOESN'T WORK, YOU CAN INFER FROM THAT RESULT THAT A PARTICULAR SEQUENCE WAS PRESENT. AND YOUR CONTROL FOR THAT IS TO DO PCR.

Q. MAYBE YOU COULD DEMONSTRATE YOUR REACTION USING THESE PIECES THAT YOU'VE BEEN USING IN YOUR OTHER DEMONSTRATIONS.

(PAUSE IN PROCEEDINGS)

THE WITNESS: IF ONE WANTED TO DETECT A PARTICULAR SEQUENCE, AS WE'VE HEARD, WE CAN DO PCR, TO AMPLIFY THE SEQUENCE BY FIRST DENATURING, THEN ADDING PRIMERS THAT ARE APPROPRIATE,

AND THEN PRIMER EXTENSION. THAT'S WHAT PCR IS, AND WE'VE GONE OVER THAT.

NOW, IF THIS PARTICULAR NUCLEOTIDE WAS A T FOR EXAMPLE, THEN NOTHING HAPPENS (INDICATING).

AND WE CALLED THIS PROCESS ALLELE-SPECIFIC PCR BECAUSE THE -- IT IS A PROCESS WHERE PCR IS BLOCKED BY CHANGING THE -- IN THE TEMPLATE.

Q. (BY MR. PASAHOW) SO YOU PUT IN THE USUAL PCR PRIMERS; IS THAT RIGHT?

A. YOU PUT IN PRIMERS SPECIFIC FOR THE SEQUENCE ONE WANTED TO DETECT.

Q. YES.

A. YEAH.

Q. USUAL PCR PRIMERS. THERE'S NOTHING DIFFERENT ABOUT THEM CHEMICALLY.

A. WELL, THEY'RE PRIMERS FOR A PARTICULAR SEQUENCE --

Q. YES.

A. -- OKAY?

Q. SO IF THAT SEQUENCE IS PRESENT, THEN THEY'LL DO A PCR REACTION.

A. THEN YOU'LL GET PCR. THAT'S OBVIOUS.

Q. JUST AS DESCRIBED IN THE CETUS PATENT?

A. YES.

Q. AND THE POINT OF YOUR PATENT WAS, IF THIS PARTICULAR BASE RIGHT HERE (INDICATING) DOESN'T MATCH UP TO THIS (INDICATING),

THEN THIS PRIMER CAN'T SIT DOWN ALL THE WAY?

A. OR IN SOME OTHER WAY INTERFERES WITH -- WE DON'T KNOW THE MECHANISM. IT -- IT EITHER CAN'T SIT DOWN OR IF THE ENZYME DOESN'T LIKE THAT PARTICULAR COMBINATION AND JUST WON'T CONTINUE.

Q. AND THE POINT OF YOUR PATENT WAS, IF -- IF THERE'S A DIFFERENCE HERE, YOU DON'T GET PCR, WHEREAS IF IT'S THE SAME, YOU DO -- IF IT'S COMPLEMENTARY, YOU DO GET PCR.

A. YEAH. I MEAN, THE CETUS PATENT HAD DESCRIBED -- AND I THINK I EXPLAINED THAT CLAIM, WHERE IF THERE WAS A NUCLEOTIDE DIFFERENT BETWEEN THE COMPLEMENTARY STRAND AND THE -- AND THE PRIMER, YOU WOULD GET PCR. IT'S SURPRISING THAT YOU DON'T IF IT'S POSITIONED IN THIS POSITION.

Q. IT HAS TO BE POSITIONED RIGHT THERE AT THE END.

A. I HAVEN'T INVESTIGATED ALL POSSIBILITIES. WE'VE LOOKED AT ALL OF THE END POSITIONS; OTHER PEOPLE HAVE LOOKED AT OTHER POSITIONS.

Q. NOW, DOES -- DOES THE CETUS -- YOU CAN TAKE YOUR SEAT.

A. (WITNESS RESUMES WITNESS STAND.)

Q. DOES THE -- DOES THE CETUS PATENT POINT OUT THAT YOU HAVE TO USE PRIMERS THAT ARE SUFFICIENTLY COMPLEMENTARY TO THE SEQUENCE IN ORDER FOR THE PCR REACTION TO WORK?

A. THAT'S -- I THINK THAT'S THE LANGUAGE THAT WE'VE BEEN HEARING.

Q. WELL, YOU DIDN'T DISCOVER THE FACT THAT YOU COULD HAVE --