THE COURT: YES.

MR. PASAHOW: YOUR HONOR, I HAVE THREE EXHIBITS FROM THE EXAMINATION I NEED TO OFFER:

THE FIRST IS EXHIBIT 172, WHICH IS A PARAGRAPH FROM THE KLEPPE ARTICLE.

THE SECOND IS EXHIBIT 173, WHICH IS THAT PARAGRAPH FROM THE PANET ARTICLE.

THE LAST IS EXHIBIT 179, WHICH IS THE COVER OF SCIENCE FROM DECEMBER 22ND 1989.

MR. FIGG: NO OBJECTION, YOUR HONOR.

THE COURT: THEY'RE ADMITTED.

(DEFENDANT'S EXHIBITS B-172, B-173, B-179 RECEIVED IN EVIDENCE)

THE CLERK: THOSE HAVE B'S IN FRONT OF THEM?

MR. PASAHOW: YES.

THE COURT: AND YOU'RE READY TO CALL YOUR NEXT WITNESS?

MR. FIGG: YES, YOUR HONOR. WE CALL DR. BRUCE WALLACE.

ROBERT BRUCE WALLACE

HAVING BEEN FIRST DULY SWORN, WAS EXAMINED AND TESTIFIED AS FOLLOWS:

THE WITNESS: I DO.

THE CLERK: PLEASE STATE YOUR FULL NAME AND SPELL YOUR LAST NAME FOR THE COURT.

THE WITNESS: ROBERT BRUCE WALLACE, W-A-L-L-A-C-E.

DIRECT EXAMINATION

BY MR. FIGG:

Q. HELLO, DR. WALLACE.

A. GOOD MORNING.

Q. DR. WALLACE, I'D LIKE TO HAND YOU A COPY OF A DOCUMENT WE'VE MARKED FOR IDENTIFICATION AS EXHIBIT A-75. CAN YOU IDENTIFY THAT FOR THE JURY?

A. YES, THAT'S A COPY OF MY CURRICULUM VITAE, SPELLING OF MY EDUCATION AND MY ACADEMIC APPOINTMENTS AND MY PUBLICATIONS.

Q. CAN YOU JUST BRIEFLY SUMMARIZE FOR THE JURY YOUR EDUCATIONAL BACKGROUND?

A. CERTAINLY. I HAVE A BACHELORS DEGREE IN BIOCHEMISTRY, WHICH I RECEIVED IN 1972, AND A PHD IN BIOCHEMISTRY I RECEIVED IN 1975. MY PHD ENCOMPASSED WORK ON DNA AND RNA FROM ANIMAL CELLS.

AND THEN I MOVED TO THE CALIFORNIA INSTITUTE OF TECHNOLOGY WHERE I DID THREE YEARS OF POST-DOCTORATE IN DR. JAMES BONNER'S LABORATORY. AND THERE AGAIN I WORKED ON SOMETHING CALLED CHROMATIN, WHICH IS THE FORM IN WHICH DNA EXISTS INSIDE CELLS.

Q. FOLLOWING YOUR POST-DOCTORAL POSITION CAN YOU DESCRIBE YOUR PROFESSIONAL BACKGROUND AND EXPERIENCE?

A. YES. IN 1978 I MOVED TO THE CITY OF HOPE MEDICAL CENTER IN DUARTE, CALIFORNIA, WHERE I STILL AM TODAY. I TOOK UP A POSITION OF RESEARCH SCIENTISTS; EXPECTED TO CONDUCT BASIC RESEARCH, OBTAIN FUNDING FROM GOVERNMENT SOURCES AND SO ON AND

TO PURSUE A RESEARCH CAREER.

AND MY CAREER WAS REALLY STARTED WHILE I WAS STILL AT CAL TECH. I WAS INVOLVED AT THAT TIME WITH SYNTHETIC DNA OLIGONUCLEOTIDES, WHICH YOU'VE HEARD MUCH ABOUT ALREADY. AND I BEGAN ESTABLISHING A LABORATORY TO INVESTIGATE THE PROPERTIES OF OLIGONUCLEOTIDES IN SOMETHING CALLED HYBRIDIZATION, WHICH YOU'LL HEAR ABOUT A LITTLE BIT LATER ON.

I'VE SPENT THE MAJORITY OF MY CAREER SINCE THAT TIME STUDYING OLIGONUCLEOTIDES AND THEIR USE IN VARIOUS APPLICATIONS INCLUDING PRIMER EXTENSIONS.

Q. WHAT IS IS THE CITY OF HOPE?

A. CITY OF HOPE IS A NONPROFIT MEDICAL CENTER. IT'S COMPOSED OF A HOSPITAL WHICH TREATS PATIENTS, CALLED THE CITY OF HOPE MEDICAL CENTER. AND IT'S COMPOSED OF, IN ADDITION, A RESEARCH INSTITUTE CALLED THE BECKMAN RESEARCH INSTITUTE.

I WORK IN THE BECKMAN RESEARCH INSTITUTE. I'M CURRENTLY CHAIRMAN OF THE DIVISION OF BIOLOGY OF THAT RESEARCH INSTITUTE. THE GOALS OF THE RESEARCH INSTITUTE ARE TO CONDUCT BASIC RESEARCH IN BIOMEDICAL, IN THE FIELD OF BIOMEDICAL RESEARCH AND MY DIVISION CONDUCTS RESEARCH PRIMARILY IN THE AREA MOLECULAR BIOLOGY.

Q. DOCTOR, HAVE YOU RECEIVED ANY HONORS OR AWARDS FOR YOUR SCIENTIFIC ACCOMPLISHMENTS?

A. WELL, OVER THE YEARS I'VE RECEIVED SEVERAL SCHOLARSHIPS AND FELLOWSHIPS TO SUPPORT MY TRAINING BOTH AS AN UNDERGRADUATE AND

AS A GRADUATE STUDENT AND LATER THEN AS A POST-DOCTORAL FELLOW AND MORE RECENTLY I RECEIVED AN AWARD FROM A GERMAN FOUNDATION TO SUPPORT A YEAR OF RESEARCH THAT I DID IN GERMANY.

Q. DR. WALLACE, YOU'RE FAMILIAR WITH THE '202 AND '195 PATENTS THAT WE'VE BEEN TALKING ABOUT?

A. YES, I AM.

Q. CAN YOU SUMMARIZE THOSE ASPECTS OF YOUR EXPERTISE WHICH PARTICULARLY BEAR ON THE SUBJECT MATTER OF THOSE PATENTS, JUST BRIEFLY SUMMARIZE THEM AT THIS POINT?

A. WELL, I'M VERY FAMILIAR WITH, AS I SAID, OLIGONUCLEOTIDES, SHORT PIECES OF DNA AND THEIR APPLICATION IN PRIMER EXTENSION REACTIONS AND THEIR APPLICATION IN SOMETHING CALLED HYBRIDIZATION, WHICH WE'LL TALK ABOUT IN A MINUTE, AS WELL AS IN THE POLYMERASE CHAINING REACTION.

Q. HAVE YOU HAD PERSONAL EXPERIENCE WITH THE POLYMERASE CHAIN REACTION?

A. YES, I HAVE. MANY PEOPLE IN THE LABORATORY HAVE BEEN INVOLVED IN THE POLYMERASE CHAIN REACTION. I'VE DIRECTLY SUPERVISED THEM IN CONDUCTING THOSE EXPERIMENTS.

Q. THESE PEOPLE IN YOUR LABORATORY WOULD BE SCIENTISTS WORKING UNDER YOU IN THE LABORATORY?

A. YES, SCIENTISTS, POST-DOCTORAL FELLOWS AND TECHNICIANS WORK UNDER MY DIRECTION.

Q. I HAND YOU A COPY OF THE '202 PATENT, WHICH HAS PREVIOUSLY BEEN ENTERED AS EXHIBIT NUMBER A-1.

DOCTOR, ARE YOU FAMILIAR -- YOU'RE FAMILIAR WITH THAT PATENT? I THINK WE'VE ALREADY ESTABLISHED THAT.

A. YES, I AM.

Q. ARE YOU FAMILIAR WITH THE ARTICLE BY KLEPPE, ET AL. THAT WAS PUBLISHED IN 1971 THAT'S BEEN MARKED . . . ALL RIGHT, AS EXHIBIT A-18.

A. YES, I AM.

Q. ARE YOU ALSO FAMILIAR WITH THE PANET PAPER PUBLISHED IN 1974 THAT'S BEEN MARKED AS EXHIBIT A-19?

A. YES, I AM.

Q. AND, LASTLY, ARE YOU FAMILIAR WITH EXHIBIT A-17, THE KHORANA NSF GRANT?

A. YES, I AM.

Q. HAVE YOU FORMED AN OPINION AS TO WHETHER OR NOT THE KLEPPE PAPER DESCRIBES THE SAME PROCEDURE THAT IS CLAIMED IN CLAIM 1 OF THE '202 PATENT?

A. YES, I HAVE.

Q. WHAT IS THAT OPINION?

A. THE KLEPPE ARTICLE SETS OUT THE SAME PROCESS AS DESCRIBED IN CLAIM 1, WITH THE -- EXACTLY THE SAME STEPS AND EXACTLY THE SAME ORDER.

Q. HAVE YOU FORMED AN OPINION AS TO WHETHER DR. KHORANA'S NSF GRANT DESCRIBES THE SAME PROCEDURE AS THAT COVERED IN THE CLAIM 1 OF THE '202 PATENT?

A. YES, I HAVE.

Q. WHAT IS THAT OPINION?
A. THAT ALSO PROVIDES THE SAME PROCESS WITH EXACTLY THE SAME STEPS AND THE SAME ORDER. AND IN ADDITION PROVIDES A DIAGRAM TO GUIDE ONE IN THAT UNDERSTANDING THAT PROCESS.
Q. HAVE YOU FORMED AN OPINION AS TO WHETHER THE PANET PAPER DESCRIBES THE SAME PROCEDURE THAT IS CLAIMED IN CLAIM 1 OF THE '202 PATENT?
A. WELL, THE PANET PAPER DESCRIBES IN THE DISCUSSION SECTION, AS DOES THE KLEPPE ARTICLE, THIS SAME PROCESS. AND IT DESCRIBES THE SAME PROCESS WITH THE SAME STEPS AND THE SAME ORDER.
Q. HAVE YOU FORMED AN OPINION -- LET ME BACK UP.

I'LL REFER TO THESE THREE DOCUMENTS AS THE, COLLECTIVELY AS THE KHORANA PRIOR ART, AND WE MAY TALK ABOUT THEM INDIVIDUALLY AS WE GO ON.

HAVE YOU FORMED AN OPINION AS TO WHETHER THE DESCRIPTIONS IN EACH OF THE THREE PIECES OF KHORANA PRIOR ART WOULD HAVE ENABLED A SCIENTIST OF ORDINARY SKILL IN THIS FIELD IN 1984 TO SUCCESSFULLY PRACTICE A PROCESS ENCOMPASSED BY CLAIM 1 OF THE '202 PATENT?
A. YES, IT IS MY OPINION THAT IN 1984 SCIENTISTS OF ORDINARY SKILL WOULD HAVE BEEN ABLE TO PRACTICE THIS PROCESS.
Q. DOCTOR, WHEN I SAY 1984 IN THESE QUESTIONS, I'M REFERRING TO PRIOR TO MARCH OF 1984. WOULD YOUR ANSWER BE THE SAME WITH THAT QUALIFICATION?
A. IT WOULD. MUCH OF THE WORK FROM 1971, LET'S SAY, LIKE THE

KLEPPE ARTICLE, THROUGH THE BEGINNING OF 1984 WOULD HAVE GIVEN SOMEBODY SUBSTANTIAL AMOUNT OF BACKGROUND IN THESE AREAS, THE PRIMER EXTENSION AND SO ON. AND, YES, MY ANSWER WOULD STILL BE THE SAME.

Q. NOW, WE'VE HEARD A LOT ABOUT A TERM CALLED PCR OR POLYMERASE CHAIN REACTION, YOU INDICATE YOU HAD EXPERIENCE WITH THAT REACTION, CAN YOU EXPLAIN TO THE JURY HOW YOUR UNDERSTANDING OF PCR RELATES TO WHAT IS COVERED BY CLAIM 1?

A. WELL, CLAIM 1 IS A VERY BROAD STATEMENT OF THE CONCEPTS BEHIND PCR. IT CAN BEGIN WITH AS LITTLE AS ONE NUCLEIC ACID SEQUENCE, AS IT SAYS AS THE BEGINNING, OR IT CAN BE A COMPLEX MIXTURE, IT CAN USE THOUSANDS OF CYCLES OR IT CAN USE JUST TWO CYCLES.

SO THIS A BROAD STATEMENT OF THE CONCEPTS BEHIND PCR AND WHAT WE KNOW OF PCR TODAY IS A GENERALLY MORE COMPLEX, GENERALLY A LARGER NUMBER OF STEPS OF CYCLES.

Q. PCR TODAY IS KNOWN THAT WAY?

A. PCR TODAY, BUT THIS IS A STATEMENT WHICH IS VERY BROAD AND GENERAL.

Q. DR. WALLACE, CAN YOU EXPLAIN TO THE JURY WHAT THE BASIS IS FOR YOUR OPINION THAT EACH OF THE KHORANA PRIOR ART ARTICLES WOULD HAVE ENABLED AN ORDINARY SKILLED SCIENTIST TO PRACTICE THIS PROCESS PRIOR TO MARCH OF '84 -- PRIOR TO MARCH OF 1984?

A. YES. WELL, FIRST OF ALL, THE KHORANA PRIOR ART DESCRIBES THIS PROCESS. IT DESCRIBES TAKING A DUPLEX DNA TEMPLATE,

DENATURING THE DNA, THE PRESENCE OF PRIMERS, EXTENDING THE PRIMERS TO GIVE A DOUBLING OF THE ORIGINAL NUMBER OF TEMPLATES AND THEN TO REPEAT THAT PROCESS. THAT'S THE BASIC PROCESS OF PCR AND IT'S DESCRIBED AS KHORANA.

IN 1984 THESE PROCESSES OF, FOR EXAMPLE,, PRIMER EXTENSION WAS ROUTINE. IT WAS IN THE LABORATORY. IT WAS COMMONPLACE TO DO A PRIMER EXTENSION IN, FOR EXAMPLE, DNA SEQUENCING REACTIONS, WHICH YOU'VE HEARD SOMETHING ABOUT. IN MUTAGENESIS EXPERIMENTS, I MAY GO INTO IN A LITTLE BIT MORE DETAIL IN A FEW MINUTES.

IN CDNA SYNTHESIS THAT'S BIOTECHNOLOGY TECHNIQUE FOR PRODUCING DNA AND IN A FORM WHICH CAN BE INTRODUCED INTO BACTERIA. AND PRIMER EXTENSIONS THEMSELVES ARE OFTEN USED AS AN ANALYTICAL TECHNIQUE.

FOR EXAMPLE, IN MOST LABORATORIES IN 1984, BEGINNING OF 1984 THEY PROBABLY WOULD HAVE HAD DNA POLYMERASE IN THEIR FREEZER.

Q. THIS TERM CDNA SYNTHESIS YOU USED, IS THAT SOMETHING THAT'S ASSOCIATED WITH GENTIC ENGINEERING OR GENE SPLICING AS IT'S SOMETIMES CALLED?

A. YES. BASICALLY PROBABLY NEED TO BACK UP A LITTLE BIT. AS WE HEARD A GENE DOESN'T ACT DIRECTLY, IT'S THE HEREDITARY MATERIAL. BUT THE GENE IS DECODED OR TURNED ON AND IS USED, THE GENE IS USED AS A TEMPLATE FOR THE PRODUCTION OF SOMETHING CALLED A MESSENGER RNA. AND THIS MESSENGER RNA IS THE

INFORMATIONAL MOLECULE WHICH DIRECTS THE SELL TO PRODUCE A PROTEIN OR ENZYME FROM THAT MESSENGER RNA.

MANY OF THE MESSENGER RNA'S WERE OF COMMERCIAL VALUE. CAN IMAGINE GROWTH HORMONE, INTERFERON, THERE'S A WHOLE LIST OF COMMERCIALLY VALUABLE PROTEINS THAT ONE WOULD HAVE WANTED TO MAKE BY GENETIC ENGINEERING.

AND CDA SYNTHESIS WAS A LABORATORY TECHNIQUE WHICH ALLOWED YOU TO TAKE THE MESSENGER RNA AND CONVERT IT INTO A DOUBLE STRANDED DNA, AS YOU HEARD A LOT ABOUT, WHICH IS THE -- WHICH IS NECESSARY TO INTRODUCE THAT IN TO BACTERIA TO ALLOW THE BACTERIA TO DIRECT THE PRODUCTION OF THOSE INTERESTING PROTEINS.

Q. THAT USED A PRIMER EXTENSION REACTION?

A. YEAH. THE FIRST . . . STRAND SYNTHESIS IT'S CALLED WHICH IS THE COPYING OF THE MESSENGER RNA USES A DNA POLYMERASE AND A PRIMER EXTENSION.

Q. YOU'VE MENTIONED A NUMBER OF USES OF DNA POLYMERASE AND PRIMER EXTENSION, INCLUDING THE ONE YOU JUST DESCRIBED, DID SCIENTISTS OF ORDINARY SKILL IN 1984 KNOW HOW TO ADJUST THE CONDITIONS OF THOSE REACTIONS TO ACHIEVE OPTIMAL OR GOOD RESULTS?

A. YES. YOU WOULD CALL IT ROUTINE EXPERIMENTATION. IF A REACTION DIDN'T PRODUCE THE DESIRED RESULT WE WERE WELL ABLE IN 1984 TO MONITOR HOW WELL A PARTICULAR REACTION WOULD HAVE WORKED. YOU WOULD HAVE BEEN IN A POSITION TO MODIFY THE CONDITIONS OF THE EXPERIMENT BY THROUGH ROUTINE EXPERIMENTATION

TO OPTIMIZE THE REACTION.

Q. WE'VE HEARD THAT THE PROCESS COVERED BY THE '202 PATENT INVOLVES USING PRIMERS AND STICKING THEM TO SOMETHING THAT'S CALLED A TEMPLATE MOLECULE, DID SCIENTISTS OF ORDINARY SKILL KNOW HOW TO ADJUST CONDITIONS FOR THAT IN 1984?

A. YES, THE -- THE UNDERSTANDING OF HOW PRIMERS STICK TO THEIR TEMPLATE WAS WELL UNDERSTOOD IN 1984. A LOT OF MY OWN RESEARCH INVOLVED THAT VERY PROCESS OF STICKING MOLECULES OF SHORT SYNTHETIC DNA MOLECULES TO THE TEMPLATE DNA'S AND UNDERSTANDING HOW THAT INTERACTION WAS -- WHAT PARAMETERS CONTROLLED IT, THE LENGTH OF THE PRIMER, THE COMPOSITION OF THE PRIMER IN TERMS OF HOW MANY A'S AND T'S AND G'S AND C'S THAT WERE IN IT AND SO ON.

Q. DID YOU PUBLISH THAT RESEARCH OF YOUR OWN?

A. YES, THERE'S SEVERAL PUBLICATIONS.

Q. THOSE PUBLICATIONS WERE PRIOR TO MARCH OF 1984; IS THAT RIGHT?

A. YES, I HAD MANY PUBLICATIONS PRIOR TO MARCH OF 1984 AND OBVIOUSLY MANY SINCE.

Q. WE'VE ALSO HEARD TALK ABOUT THE USE OF THE PROCESS DESCRIBED HERE OF SYNTHETIC DNA, DNA CHEMICALLY SYNTHESISED, CAN YOU COMMENT ON WHETHER SYNTHETIC DNA WAS AVAILABLE TO SCIENTISTS OF ORDINARY SKILL IN 1984?

A. IN 1984 DNA, SYNTHETIC DNA WAS REALLY AVAILABLE TO MANY SCIENTISTS, NOT ALL SCIENTISTS, THROUGH AUTOMATED INSTRUMENTATIONS. THERE WERE INSTRUMENTS YOU COULD PURCHASE

WHICH ALLOWED YOU TO SYNTHESIS DNA AT THE PUSH OF A BUTTON.

ALSO, THERE WAS MANY PUBLISHED PROCEDURES WHICH TOLD YOU HOW TO SYNTHESIZE DNA IF YOU DIDN'T A MACHINE. BUT NOT EVERY LABORATORY, EVEN IN 1984, PROBABLY HAD ACCESS TO SUCH MACHINES. THEY WERE EXPENSIVE.

THEN THEY WOULD HAVE TO HAVE RESORTED TO BUYING IT THROUGH A COMMERCIAL SUPPLY HOUSE, FOR EXAMPLE, THROUGH PAYMENT POLICY, SO MANY DOLLARS FOR SUCH AND SUCH AND TYPE.

Q. WHEN YOU SAY BUY IT FROM A COMMERCIAL SUPPLY HOUSE, YOU MEAN BUY SYNTHETIC DNA?

A. A PARTICULAR SYNTHETIC DNA.

Q. COULD THEY DESIGN THEIR OWN SYNTHETIC DNA THEN AND ORDER IT FROM THE SUPPLY HOUSE?

A. YES. IN 1984, YES, THEY COULD.

Q. NOW, I BELIEVE CITY OF HOPE HAS HAD RATHER UNIQUE POSITION WITH RESPECT TO SYNTHETIC DNA; IS THAT RIGHT?

A. THAT'S CORRECT.

Q. AND IN YOUR RESEARCH IN THE LATE '70S, DID YOU HAVE -- HOW WOULD YOU COMPARE THE AVAILABILITY OF SYNTHETIC DNA FOR YOUR OWN RESEARCH TO THE AVAILABILITY OF SYNTHETIC DNA TO PEOPLE WHO DIDN'T WORK IN A PLACE LIKE CITY OF HOPE?

A. MAYBE I SHOULD BACK UP A MINUTE AND SAY THAT IT WAS REALLY THE WORK OF DR. KHORANA WHICH GOT THE WHOLE THING GOING. HE REALLY SHOWED THE FEASIBLY OF MAKING PIECES OF SYNTHETIC DNA OF ANY SUBSTANTIAL LENGTH.

FOLLOWING HIS WORK THERE WAS MANY RESEARCHERS THAT WORKED IN THE AREA OF DNA SYNTHESIS, UNDERSTANDING HOW TO CHEMICALLY PUT THESE BUILDING BLOCKS TOGETHER. AND ONE OF THOSE RESEARCHERS WAS DR. KEIICHI ITAKURA, HE MOVED TO THE CITY OF HOPE IN ABOUT 1978, ABOUT THE SAME TIME I DID.

SO HE WAS AT THE CITY OF HOPE WHEN I CAME AND IT WAS THROUGH MY RELATIONSHIP WITH HIM AND HIS LABORATORY, WHICH HAD THE SKILLS TO ASSEMBLE SYNTHETIC DNA, THAT I HAD ACCESS TO SYNTHETIC DNA AS EARLY AS 1978 AND ACTUALLY PROBABLY 1977, EVEN BEFORE I MOVED TO THE CITY OF HOPE WHILE I WAS STILL AT CAL TECH.

THIS WAS KIND OF A SPECIAL CASE BECAUSE NOT EVERYBODY WOULD HAVE HAD ACCESS TO IT, BUT SINCE I HAD ACCESS TO DR. ITAKURA'S LABORATORY AND THEIR SKILLS I HAD ACCESS TO SYNTHETIC DNA.

AS TIME WENT ON THEN FROM 1978 ONWARDS TOWARDS 1980, EARLY '80S, OR THE SYNTHETIC DNA THAT I USED WAS PRODUCED IN DR. ITAKURA'S LABORATORY, AND WE WOULD ACKNOWLEDGE THEIR CONTRIBUTION TO THE RESEARCH EFFORT IN A PARTICULAR PUBLICATION THAT CAME OUT OF THEIR SUPPLYING SYNTHETIC DNA BY PUTTING THOSE CHEMISTS' NAMES ON THE SCIENTIFIC PUBLICATION.

Q. DID THERE COME A TIME WHEN YOU STOPPED PUTTING A CHEMIST'S NAME ON A PUBLICATION IF THAT PERSONS ONLY CONTRIBUTION WAS SYNTHESIZING THE DNA?

A. WELL, LATER ON IT BECAME POSSIBLE FOR MY OWN LABORATORY TO

SYNTHESIZE THEIR OWN DNA THROUGH MANUAL PROCEDURES. I COULDN'T AFFORD TO BUY AN AUTOMATED INSTRUMENT, BUT I COULD DO MANUAL SYNTHESIS IN THE LABORATORY, BUT THAT WAS A SHORT LIVED PERIOD.

THEN THE CITY OF HOPE SET UP SOMETHING CALLED -- A FACILITY, A LABORATORY WHOSE JOB IT IS TO MAKE SYNTHETIC DNA FOR OTHERS FOR A COST, NOT FOR A PROFIT. SIMPLY TO PASS THE COST OF THAT EFFORT ON TO THE INVESTIGATOR, THAT'S THE SITUATION THAT FOR MOST INVESTIGATORS AT THE CITY OF HOPE THEY PURCHASED THEIR DNA'S THROUGH THIS FACILITY.

LAST YEAR, FOR EXAMPLE, I THINK THEY MADE IN EXCESS OF 600 OLIGONUCLEOTIDES FOR THE RESEARCHERS AT THE CITY OF HOPE.

Q. OLIGONUCLEOTIDE IS A SHORT PIECE OF DNA?

A. OLIGO MEANS SHORT, THESE ARE SHORT PIECES OF DNA.

Q. SUCH AS THE THINGS THAT ARE USED AS PRIMERS IN THE PROCESS DESCRIBED HERE?

A. SUCH AS THOSE THINGS. EVEN RECITES THE WORD OLIGONUCLEOTIDE IN STEP A.

Q. YES. IN SEVERAL OF MY QUESTIONS I'VE USED THE TERM PERSON OF ORDINARY SKILL IN THE ART IN 1984. WERE YOU IN THE COURTROOM WHEN DR. KORNBERG GAVE THE DESCRIPTION OF SUCH A PERSON?

A. YES, I WAS.

Q. DO YOU AGREE WITH THE DESCRIPTION OF THE PERSON OF ORDINARY SKILL IN THE ART IN 1984 THAT DR. KORNBERG GAVE?

A. YES, I DO.

Q. NOW, AGAIN, DR. WALLACE, FOCUSING ON THE PERIOD OF AROUND

FEBRUARY OR MARCH OF 1984, IN YOUR OPINION DOES THE PROCESS DESCRIBED IN CLAIM 1 OF THE '202 PATENT INVOLVE ANY NEW TECHNIQUES OR PROCEDURES; IN OTHER WORDS, ARE ANY OF THE COMPONENT PARTS OF THIS NEW?

A. NO. THE PROCEDURES, AS I SAY, WERE STANDARD LABORATORY PROCEDURES. BASICALLY THE PROCESSES OF DENATURATION. PRIMER EXTENSION FOLLOWED BY ANOTHER CYCLE OF DENATURATION AND PRIMER EXTENSION.

Q. I'D LIKE FOR YOU TO VISUALIZE A REACTION COVERED BY THIS CLAIM, WHICH STARTS WITH A DNA MOLECULE, LET'S SAY, OF 50 BASE NUCLEOTIDES IN LENGTHS WITH TWO PRIMERS, SAY, 15 NUCLEOTIDES IN LENGTH THROUGH -- AND RUNNING IT THROUGH TWO OR THREE CYCLES OF HEATING, COOLING AND PRIMER EXTENSION, CAN YOU DESCRIBE TO THE JURY HOW A PERSON OF ORDINARY SKILL PERFORMING SUCH A REACTION IN EARLY 1984 WOULD HAVE GONE ABOUT SETTING UP AND PERFORMING THAT REACTION?

A. WELL, IN THAT PARTICULAR CASE OF YOUR HYPOTHETICAL OF 50 NUCLEOTIDE MOLECULE OF DNA. FIRST OF ALL, YOU HAVE TO DETERMINE ITS SEQUENCE IF IT WASN'T ALREADY KNOWN. SO YOU WOULD NEED TO KNOW THE SEQUENCE OF THE TEMPLATE, AT LEAST IN THE REGIONS IN WHICH YOU'RE GOING TO DESIGN THE PRIMER.

YOU THEN WOULD GO TO THE FACILITY THAT COULD PRODUCE THE OLIGONUCLEOTIDE PRIMER FOR YOU AND YOU WOULD HAVE YOUR PRIMER SYNTHESIZED, TWO PRIMERS IN ORDER TO ACCOMPLISH THIS AMPLIFICATION PROCESS.

YOU WOULD THEN ASSEMBLE A REACTION USING PROBABLY THE COMPONENTS OF A PRIMER EXTENSION REACTION AS YOU KNEW THEM TO EXISTS IN THE LITERATURE, IN THE SCIENTIFIC PUBLICATIONS. THERE ARE MANY PUBLICATIONS WHICH DESCRIBE USING PRIMERS ON TEMPLATES.

AND SO YOU PROBABLY WOULD HAVE CHOSEN SUCH A SOLUTION WHICH CONTAINS SALTS, SOMETHING CALLED MAGNESIUM WHICH IS REQUIRED BY THE ENZYME, AN AGENT TO CONTROL THE ACIDITY, SOMETHING CALLED BUFFER AND YOU WOULD ASSEMBLE THIS REACTION.

YOU WOULD HAVE CHOSEN HEAT AS THE METHOD TO SEPARATE THE STRANDS BECAUSE THAT WAS COMMONLY THE WAY WE DID IT. YOU WOULD THEN HEAT THE STRANDS IN THE PRESENCE OF THE PRIMERS. YOU WOULD HAVE COOLED THE REACTION, ADDED THE DNA POLYMERASE, ALLOWED THE REACTION TO PROCEED, A PRIMER EXTENSION REACTION UNDER CONDITIONS AS I SAID WHICH WERE COMMONLY USED IN THE LABORATORY.

YOU WOULD PROBABLY THEN AT THAT POINT DONE AN INTERIM ANALYSIS TO BE SURE THE EXPERIMENT WORKED AND WE'VE HAD MANY WAYS TO DO THAT. FOR EXAMPLE, USING GELOELECTROPHORESIS (PHONETIC), YOU COULD HAVE ANALYZED THE INTERIM PRODUCT AND THEN YOU WOULD HAVE REPEATED THE WHOLE PROCESS OF DENATURATION IN THE PRESENCE OF THOSE PRIMERS, IN ADDITION A COOLING STEP. THEN THE ADDITION OF THE DNA POLYMERASE TO ACCOMPLISH ANOTHER ROUND OF PRIMER EXTENSION. AT THE END OF THAT YOU WOULD HAVE HAD A TWO DOUBLINGS OR THE CONVERSION OF ONE DNA MOLECULE TO FOUR DNA MOLECULES.

Q. DR. WALLACE, IN THE HYPOTHETICAL I GAVE YOU WHICH SAID ASSUME THE PRIMERS ARE ABOUT 50 NUCLEOTIDES LONG, WHAT IF I HADN'T GIVEN THAT CONDITION IN MY HYPOTHETICAL, HOW WOULD A PERSON OF ORDINARY SKILL IN 1984 HAVE KNOWN HOW LONG TO MAKE THE PRIMERS?

A. WELL, PRIMER LENGTHS WOULD HAVE BEEN KNOWN FOR MANY THINGS IN THE LITERATURE. AS DR. KORNBERG ALREADY TESTIFIED MUCH OF HIS OWN WORK RELATED TO THAT. THE KLEPPE PAPER IN FACT RELATED TO THAT ISSUE, BUT PROBABLY MORE IMPORTANTLY PEOPLE WERE USE TO USING PRIMERS TO DO DNA SEQUENCING.

NOW, THAT'S A PROCESS THAT USERS PRIMER EXTENSION IN ORDER TO DETERMINE THE ORDER OF THE BUILDING BLOCKS IN THE TEMPLATE. THAT PROCESS IS THE PROCESS OF PRIMER EXTENSION AND IT WAS WELL-KNOWN THAT PRIMERS OF 10, 15 OR 25, 25 NUCLEOTIDES IN LENGTH COULD BE USED FOR THAT PROCESS. SO YOU WOULD HAVE HAD A BASIS FOR DESIGNING THE ORIGINAL PRIMERS IN ANY EVENT.

Q. WHAT ENZYME WOULD THIS PERSON OF ORDINARY SKILL HAVE BEEN LIKELY TO HAVE CHOSEN FOR THE REACTION IN 1984?

A. WELL, IN 1984 THE ENZYME OF CHOICE PROBABLY WOULD HAVE BEEN SOMETHING THAT'S CALLED THE KLENOW FRAGMENT OF DNA POLYMERASE 1. DNA POLYMERASE 1 IS DR. KORNBERG'S ENZYME, THE ONE HE DISCOVERED. BUT IT WAS FOUND THROUGH THE COURSE OF THE YEARS THAT THERE WAS ONE ACTIVITY, ONE OF THE DEGRADING ACTIVITIES OF THE ENZYME WOULD BE REMOVED AND THIS ACTIVITY WAS REMOVED AFTER IT PRODUCED WHAT WAS CALLED THE LARGE FRAGMENT OR THE KLENOW

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FRAGMENT OF DNA POLYMERASE 1.

THIS ENZYME WAS ROUTINELY USED AS THE ENZYME OF CHOICE AT THAT TIME FOR DNA SEQUENCING OTHER PRIMER EXTENSION REACTIONS, CDNA SYNTHESIS AND SO ON. AND IT BY THE WAY WAS COMMERCIALLY AVAILABLE.

Q. YOU SAY THAT IT HAD SOME DEGRADING ACTIVITY, WHAT DOES THAT MEAN?

A. WELL, THE ENZYME DNA POLYMERASE 1 HAD AN ACTIVITY WHICH WOULD REMOVE NUCLEOTIDES IN -- FROM THE 5 PRIME TO 3 PRIME END, WE TALKED ABOUT DNA HAVING A DIRECTION AND THE -- THIS ACTIVITY WAS ONE DESIGNED TO REMOVE THE NUCLEOTIDES IN THE 5 PRIME TO 3 PRIME DIRECTION.

AND IT WAS POSSIBLE AS IT TURNS OUT BY MECHANISMS WHICH HAVE TO DO WITH THE WAY PROTEINS EVOLVE PRESUMABLY. THAT THIS ACTIVITY WAS SEPARABLE BY MOLECULAR BIOLOGICAL MANIPULATION.

Q. SO THE ENZYME THAT YOU'RE USING SYNTHESIZE YOUR DNA ACTUALLY HAS AN ACTIVITY THAT WILL CHEW UP SOME OF YOUR DNA, IS THAT WHAT YOU'RE SAYING?

A. THE ENZYME THAT YOU'RE USING FOR THIS IN THIS HYPOTHETICAL CASE WOULD NOT HAVE THAT ACTIVITY. THERE IS ANOTHER ACTIVITY WHICH I THINK DR. KORNBERG CALLED THE EDITING ACTIVITY WHICH DEGRADES DNA FROM THE OTHER DIRECTION, BUT ONLY AS A MECHANISM OF CORRECTING ANY MISTAKES IF IT WAS PUTTING IN AN A AND SHOULD HAVE PUT IN A T, IT WILL HE REMOVE THAT MISTAKE THEN PROCEED.

Q. YOU MENTIONED THAT THIS KLENOW ENZYME WAS AVAILABLE

COMMERCIALLY IN 1984, DO YOU KNOW IF IT WAS AVAILABLE COMMERCIALLY, SAY, PRIOR TO 1975 OR BACK IN THE EARLY '70S WHEN DR. KHORANA'S GROUP WAS DOING THEIR WORK?

A. IN THE EARLY '70S IT WOULD NOT HAVE BEEN COMMERCIALLY AVAILABLE. THE KLENOW ENZYME WOULDN'T HAVE BEEN AVAILABLE IN THE EARLIEST PART OF THE '70S. I DON'T REMEMBER WHEN THE KLENOW FRAGMENT WAS REALLY FIRST DESCRIBED.

BUT, IN ANY EVENT, ANY ENZYME IN THOSE DAYS ESSENTIALLY MOST ENZYMES, CERTAINLY MOST POLYMERASE TO BE PURIFIED IN THE LABORATORY BY VERY DIFFICULT OR LONG PROCEDURES AT LEAST OR THEY HAD TO BE OBTAINED THROUGH A COLLABORATOR WHO HAD ALREADY TROUBLED HIMSELF TO DO THAT.

Q. YOU MENTIONED THE ENZYME AND DNA WOULD HAVE TO BE PUT IN THE SOLUTION, I THINK YOU CALLED IT A BUFFER?

A. YES, I DID.

Q. WAS THE -- CAN YOU COMMENT ON WHETHER OR NOT THE RECIPES FOR THESE BUFFERS WERE READILY AVAILABLE TO SCIENTISTS OF ORDINARY SKILL OR WOULD THEY HAVE TO DO A LOT OF DIGGING TO FIND OUT HOW TO PUT ONE OF THESE BUFFERS TOGETHER?

A. NO, THE COMPOSITION OF THESE REACTION MIXTURES YOU CAN CALL THEM, BUFFER REALLY A BAD NAME FOR THESE. WE CALL IT A BUFFER IN THE LABORATORY. THE BUFFER IS REALLY ONLY ONE OF THE COMPONENTS IN THE SOLUTION, BUT IN ANY EVENT THAT'S WHAT IT'S CALLED.

THE COMPOSITIONS OF SUCH SOLUTIONS WERE PUBLISHED IN

MANY PAPERS. SO ANY PAPER THAT DESCRIBED HOW THEY DID A PARTICULAR DNA SEQUENCING REACTION, FOR EXAMPLE, WOULD HAVE PUBLISHED THE RECIPE FOR THEIR SOLUTION AND THERE WERE RECOMMENDED SOLUTIONS THAT WERE PROVIDED TO THE PEOPLE PURCHASING ENZYMES THESE RECOMMENDED SOLUTIONS WERE AVAILABLE FROM THE SAME SUPPLY HOUSE THAT WAS SELLING THE ENZYME.

Q. YOU MENTIONED THAT ONE OF THE STEPS THAT THE PERSON WOULD DO IN CARRYING OUT THIS REACTION IS TO HEAT THE DNA, HOW WOULD THE PERSON KNOW HOW HOT TO HEAT IT TO?

A. WELL, IT WAS WELL-KNOWN THAT HEAT WOULD SEPARATE THE STRANDS OF THE DUPLEX DNA, AND IT WAS OFTEN NOT EVEN CONSIDERED HOW HOT ONE NEEDED TO DO IT. USUALLY YOU JUST INTRODUCE THE DNA INTO A BOILING WATER VAT, HUNDRED DEGREES CENTIGRADE WHICH IS THE TEMPERATURE FOR BOILING WATER, IS SUFFICIENT TO SEPARATE THE STRANDS OF MOST DNA MOLECULES, THAT WAS WELL-KNOWN.

Q. THIS PROCEDURE YOU'VE DESCRIBED BY WHICH THE PERSON WOULD GO ABOUT CARRYING OUT THE AMPLIFICATION OF THE 50 BASE OR 50 NUCLEOTIDE LENGTH, WOULD THE PERSON OF ORDINARY SKILL IN THE ART IN 1984 HAVE KNOWN TO FOLLOW THOSE VARIOUS STEPS THAT YOU'VE DESCRIBED FROM EACH OF THE KHORANA PRIOR ART ARTICLES THAT WE'VE BEEN DESCRIBING?

A. WELL, YES. IN MY OPINION, YES. THE ARTICLES ENLIGHTENED THE READER AS TO THE BASIC PROCESS OF PCR, WHICH IS NOW CALLED PCR. IT TELLS YOU TO ADD TWO PRIMERS TO A DUPLEX DNA, AND IT TELLS YOU TO DENATURE AND PERFORM TWO ROUNDS OF PRIMER

EXTENSION. ESSENTIALLY THE LANGUAGE OF CLAIM 1 AND YOUR BASIC, THE BASIC KNOWLEDGE OF ANY STUDENTS OF BIOCHEMISTRY IN 1984 WOULD HAVE GIVEN YOU THE KNOWLEDGE OF EXACTLY WHAT CONDITIONS OR THE CONDITIONS TO USE TO ATTEMPT TO GET THIS REACTION TO WORK.

Q. IN YOUR OPINION, WOULD A PERSON OF ORDINARY SKILL IN EARLY 1984 HAVE HAD ANY EXPECTATION OF WHETHER OR NOT THE REACTION WOULD WORK BASED UPON THE TEACHINGS OF THE KHORANA PUBLICATIONS AND OTHER INFORMATION AVAILABLE TO THAT PERSON?

A. OH, I THINK YOU WOULD HAVE EXPECTED IT TO WORK. THE -- AS I SAID, PRIMER EXTENSIONS WERE ROUTINE IN THE LABORATORY. IT WAS THE STANDARD PROCEDURE USED IN MANY LABORATORIES DAILY TO DO DNA SEQUENCING AND THOSE REACTIONS WERE QUITE EASY TO SET UP AND THEY WERE QUITE REPRODUCIBLE.

SO IT WOULD NOT HAVE SURPRISED ONE TO HAVE -- TO HAVE TAKEN THE IDEAS IN THE KHORANA PRIOR ART AND APPLIED THEM TO THIS AMPLIFICATION PROCESS AND GOTTEN IT TO WORK.

Q. LET'S ASSUME THE REACTION IS RUN AS YOU'VE DESCRIBED, AND THE FIRST TIME THE PERSON RUNS IT OPTIMAL RESULTS ARE NOT ACHIEVED. IF THAT WERE TO HAPPEN WHAT WOULD THE PERSON OF ORDINARY SKILL IN THE ART DO IN EARLY 1984?

A. IN 1984, AS I INDICATED IN MY HYPOTHETICAL CASE, YOU WOULD HAVE BEEN IN -- YOU WOULD HAVE HAD TECHNIQUES TO DETERMINE IF THE REACTION WORKED.

THERE ARE MANY WAYS IN WHICH YOU COULD HAVE DONE THAT AND YOU WOULD HAVE KNOWN HOW WELL IT WORKED. SO YOU WOULD HAVE

BEEN ABLE TO JUDGE FROM THOSE EXPERIMENTS, WHETHER IT WORKED EXTREMELY WELL OR POORLY AND FROM THAT INFORMATION YOU WOULD THEN DESIGN EXPERIMENTS TO ALTER THE REACTION IN A SYSTEMATIC WAY TO IMPROVE THE RESULTS IF NEED BE.

Q. WHAT DO YOU MEAN ALTER THE REACTION IN A SYSTEMATIC WAY, CAN YOU ELABORATE ON THAT?

A. WELL, THE REACTION CONTAINS MANY COMPONENTS. CONTAINS TEMPLATE, IT CONTAINS PRIMERS, IT CONTAINS ENZYME, IT CONTAINS BUFFERS AND IT CONTAINS THE BUILDING BLOCKS, THE NUCLEOSIDE TRIPHOSPHATES AND IT CONTAINS MAGNESIUM AND SO FORTH.

NOW, YOU KNEW THAT THE BUFFER, THE SOLUTION THAT YOU HAD CHOSEN AT THE BEGINNING SUPPORTED PRIMER EXTENSION, SO YOU WOULD HAVE EXPECTED THAT REACTION TO WORK.

BUT IF IT DIDN'T WORK OPTIMALLY YOU WOULD HAVE INVESTIGATED TEMPLATE CONCENTRATION, POLYMERASE CONCENTRATION, CONCENTRATION OF NUCLEOSIDES TRIPHOSPHATES, THE BUILDING BLOCKS TO DETERMINE IF THOSE THINGS IMPACTED THE EFFICIENCY OF THE REACTION, LET'S CALL IT, OR HOW WELL IT WORKED.

Q. WOULD YOU CHARACTERIZE THAT WORK AS SOMETHING INVENTIVE OR AS ROUTINE OPTIMIZATION OR WOULD YOU HAVE SOME OTHER CHARACTERIZATION FOR IT?

A. I WOULDN'T HAVE THOUGHT IT WOULD HAVE BEEN ANYMORE DIFFICULT OR INVENTIVE, LET'S SAY, THAN ANY OTHER PROCESS THAT WAS BEING OPTIMIZED IN THE LABORATORY. MANY OF THE OTHER PROCESSES HAD -- MANY PROCESSES IN THE LABORATORY WHEN YOU FIRST INTRODUCE THEM

HAVE TO BE MODIFIED TO SUIT YOUR OWN ENDS.
Q. DO YOU HAVE ANY FEEL FOR HOW LONG IT WOULD HAVE TAKEN SCIENTISTS OF ORDINARY SKILL IN EARLY 1984 TO HAVE WORKED OUT THE CONDITIONS FOR ACCEPTABLE RESULTS WITH THE REACTION?
A. IT'S DIFFICULT TO SAY. I MEAN, THERE ARE PEOPLE WHO COME INTO THE LAB WHO CAN DO THINGS ON THE FIRST TRY AND THINGS. PEOPLE WHO COME IN THAT AREN'T NECESSARILY AS TALENTED, BUT IF YOU TAKE THIS PERSON OF ORDINARY SKILL YOU'RE TALKING ABOUT I WOULD THINK IT WOULD HAVE TAKEN THEM ON THE ORDER OF WEEKS TO GET THIS PARTICULAR HYPOTHETICAL REACTION OPTIMIZED.
Q. TO GET IT OPTIMIZED?
A. UH-HUH.
Q. DR. WALLACE, THERE'S BEEN SOME DISCUSSION ABOUT THE STATEMENT IN THE KLEPPE PAPER ABOUT THE TEMPLATES STRANDS COMING BACK TOGETHER, DO YOU KNOW WHAT I'M TALKING ABOUT?
A. YES, I DO.
Q. HAVE YOU CONSIDERED WHETHER A SCIENTIST OF ORDINARY SKILL IN EARLY 1984 WOULD HAVE BEEN DISCOURAGED FROM TRYING THE REACTION DESCRIBED IN DR. KHORANA'S PUBLICATION BECAUSE OF THE POSSIBILITY THAT THE TWO TEMPLATES STRANDS MIGHT COME BACK TOGETHER AND PREVENT THE REACTION FROM PROCEEDING?
A. WELL, I'VE CONSIDERED THAT, OF COURSE, BUT I WOULDN'T HAVE THOUGHT ONE WOULD HAVE BEEN EVEN DISCOURAGED. THERE WERE MANY EXAMPLES OF REACTIONS, PRIMER EXTENSION REACTIONS WHICH BEGAN WITH DOUBLE STRANDED DNA TEMPLATES.

Q. MAYBE IT WOULD BE USEFUL TO EXPLAIN WHAT WE'RE TALKING ABOUT ON THAT, WITH THE HELP OF THIS POSTER THAT DR. KORNBERG USED.

A. MAY I?

THE COURT: YES, YOU MAY STEP DOWN.

(PAUSE IN THE PROCEEDINGS)

THE WITNESS: WELL, AS YOU ARE WELL AWARE THROUGH THE MANY TIMES WE'VE GONE THROUGH THIS, THAT THIS IS A DOUBLE STRANDED DNA TEMPLATE, WHICH PRIOR TO THE AMPLIFICATION REACTION HAS TO BE DENATURED OR THE STRANDS MUST BE SEPARATED, USUALLY BY HEATING BEFORE ONE CAN GET A SUITABLE PRIMER TO ANNEAL OR BIND OR STICK.

HOWEVER, ONE POSSIBILITY THAT THE KLEPPE ARTICLE WAS REALLY REFERRING TO IS THAT BEFORE THIS COULD HAPPEN THESE TWO STRANDS WOULD COME BACK TOGETHER AND PRECLUDE ANY BINDING OF THE PRIMER TO THE TEMPLATE. THEY AT LEAST CAUTION THE READER THIS IS SOMETHING TO THINK ABOUT.

AND THEY OFFERED AT LEAST ONE ANSWER TO THIS WHICH WAS TO USE LARGE EXCESSES OF PRIMER BECAUSE IF YOU USE LARGE EXCESSES OF PRIMER IT'S REASONED THAT THE PRIMER IS MORE LIKELY TO FIND ITS SITE ON THE TEMPLATE THAN THE TWO SEMIPLATE STRANDS TO FIND EACH OTHER.

I WAS TRYING TO THINK OF A GOOD ANALOGY FOR YOU, BUT IF YOU IMAGINE HAVING A BAG OF FRUIT WITH AN EQUAL NUMBER OF ORANGES AND APPLES. TO REACH INTO THE BAG YOU HAVE AN EQUAL PROBABILITY OF PULLING OUT AN ORANGE AND YOU CAN IMAGINE THAT

YOUR HAND IS THE SITE WHICH THE PRIMER IS GOING TO BIND AND THE ORANGE IS THE PRIMER, AND THE APPLES ARE THE OTHER TEMPLATE STRANDS.

IF, ON THE OTHER HAND, YOU HAVE TEN TIMES MORE ORANGES IN THAT BAG THAN APPLES, AND YOU REACH IN YOU'RE MUCH MORE LIKELY TO PULL AN ORANGE. IT'S THAT CONCEPT OF THE PRIMER BEING ABLE TO COMPETE MORE FAVORABLY FOR THE BINDING THAT IS BEING ADDRESSED.

Q. (BY MR. FIGG) DOES DR. KHORANA'S PRIOR ART LEAD ONE TO USE THIS EXCESSIVE PRIMERS?

A. YES, THE PRIOR ART EXPLICITLY SAYS THAT YOU SHOULD USE AN EXCESSIVE PRIMER. BUT I MIGHT ADD, THAT IN 1984 PRIMER EXCESSES WERE ROUTINE FOR DOING SEQUENCING REACTIONS, FOR EXAMPLE.

MR. FIGG: JUST A MOMENT, YOUR HONOR.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) WHILE WE'RE LOOKING FOR THE POSTER, DR. WALLACE, DO YOU RECALL SPECIFICALLY THE LANGUAGE IN THE NSF GRANT APPLICATION DIRECTING THE READER TO USE AN EXCESSIVE PRIMERS?

A. I BELIEVE IT SAID EXCESS, UNDERLINED IT.

Q. SO IT EMPHASIZED USING EXCESS?

A. YES.

Q. ARE YOU AWARE OF ANY OTHER LITERATURE THAT WOULD HAVE CONVINCED A SKILLED SCIENTISTS IN EARLY 1984 THAT THIS PROBLEM OF THE TEMPLATE STRANDS COMING BACK TOGETHER WOULD NOT HAVE BEEN

A PROBLEM?
A. YES, THERE WERE A NUMBER OF SCIENTIFIC PUBLICATIONS WHICH DESCRIBED DOING THIS PROCESS OF DNA SEQUENCING I TALKED ABOUT, THAT IS DETERMINING THE ORDER OF THE BUILDING BLOCK TEMPLATES.

IT WAS TRADITIONAL. IN FACT, WE HEARD THAT DOCTOR SANGER'S LAB HAD PIONEERED THIS TECHNIQUE TO USE WHAT ARE CALLED SINGLE STRANDED DNA TEMPLATES. THESE ARE TEMPLATES THAT WERE OBTAINED FROM A VIRUS WHICH INFECTS BACTERIA.

BUT THERE ARE MANY PAPERS THAT USED DOUBLE STRANDED DNA TEMPLATES, STARTED WITH DNA TEMPLATES THAT WERE DOUBLE STRANDED AND ADDED A PRIMER TO THE DOUBLE STRANDED DNA TEMPLATE AFTER THE STRANDS WERE SEPERATED BY HEATING.

AND BECAUSE YOU ONLY HAD ONE PRIMER AND A TEMPLATE YOU COULD USE THIS PRIMER, COULD DEFINE A UNIQUE END TO WHICH YOU COULD START YOUR DNA SEQUENCING REACTIONS.

Q. IT WOULD GO DOWN ONE BY ONE?
A. ONE BY ONE AND DETERMINE THE NEXT SAYS WAS A, NEXT NUCLEOTIDE WAS A C, THE NEXT ONE A G AND SO ON, DETERMINE FROM STARTING WITH DOUBLE STRAND DNA TEMPLATES.
Q. I'LL SHOW YOU A COPY OF AN ARTICLE WE'VE MARKED AS EXHIBIT A-47. CAN YOU IDENTIFY THAT ARTICLE?
A. YES, THIS IS A PUBLICATION FROM -- BASICALLY FROM MY LABORATORY BY MYSELF AND OTHERS AT THE CITY OF HOPE DESCRIBING -- IT'S ENTITLED A SET OF SYNTHETIC OLIGODEOXYRIBONUCLEOTIDE PRIMERS FOR DNA SEQUENCING IN THE

PLASMA VECTOR.

THIS IS A PAPER WHICH SHOWED THAT YOU COULD INDEED -- THAT YOU COULD INDEED USE DOUBLE STRANDED DNA TEMPLATES. OF COURSE, AFTER THEY WERE SUBJECTED TO THE DENATURATION STEP AS TEMPLATES FOR DNA SEQUENCING.

THERE'S A LOT OF LONG WORDS HERE, OLIGODEOXYRIBONUCLEOTIDES ARE WHAT -- YOU'VE HEARD OLIGO ENOUGH, CLEOTIDES SHORT PIECES OF DNA, THAT'S WHAT THE DEOXYRIBO INDICATES, SHORT PIECES OF DNA. THEY WERE SYNTHESIZED IN THE LABORATORY OF DR. ITAKURA BY TWO CHEMISTS, ONE FROM JAPAN AND ONE FROM SOMEPLACE ELSE.

AND WE USED AS TEMPLATES PLASMA VECTORS, PLASMA ARE DOUBLE STRANDED DNA MOLECULES, THEY EXIST AS CIRCLES AND THEY RESIDE NORMALLY WITHIN BACTERIA. THE FREE LIVING KIND OF DNA CIRCLES THAT ARE INSIDE BACTERIA AND OFTEN CAUSE BACTERIA TO BE ANTIBIOTIC RESISTANT.

SO THESE ARE COMMONLY USED IN BIOTECHNOLOGY MOLECULAR BIOLOGY FOR MOVING DNA OR INTRODUCING DNA INTO BACTERIA, SO THEY ARE DOUBLE STRANDED IT WOULD HAVE TO BE ABLE TO SEQUENCE THEM DIRECTLY RATHER THAN GO THROUGH MANIPULATIONS WHICH WOULD HAVE CONVERTED THEM INTO SINGLE STRANDED DNA AND THIS JUST SHOWED THAT WAS FEASIBLE.

Q. I WOULD JUST NOTE FOR THE RECORD WE'VE PLACED ON THE EASEL THE BLOW UP OF THE FIRST PAGE OF DR. WALLACE'S ARTICLE EXHIBIT A-47

DID YOU DRAW ANY CONCLUSIONS FROM THIS ARTICLE THEN AS TO YOUR ABILITY TO USE PRIMER EXTENSION WITH DOUBLE STRANDED DNA?

A. YES. PRIMER EXTENSION COULD BE USED ON DOUBLE STRANDED DNA TEMPLATES TO DETERMINE THE NUCLEOTIDE SEQUENCE THE GOALS OF THE RESEARCH WERE ACHIEVED.

Q. DID YOU FIND PROBLEMS WITH THE TEMPLATE STRANDS COMING TOGETHER AND SQUEEZING OUT THIS PRIMER PRESENTED ANY DIFFICULITIES FOR YOU?

A. IT DIDN'T APPEAR TO PRESENT ANY DIFFICULTIES AT ALL.

Q. I'D LIKE TO HAND YOU ANOTHER ARTICLE WE'VE MARKED AS EXHIBIT A-108 AND ASK YOU IF YOU CAN IDENTIFY THAT ONE?

A. YES, THIS IS ANOTHER ARTICLE BY MYSELF AND MY COLLEAGUES ENTITLED DIRECTED DELETION OF A OF A YEAST TRANSFER RNA INTERVENING SEQUENCE. IT WAS PUBLISHED IN SCIENCE IN 1980.

THIS IS RATHER A VERY COMPLEX PROCEDURE THAT WE WERE WORKING ON TO USE A GENETIC TECHNIQUE CALLED IN VITRO MUTAGENESIS. WHAT WE WANTED TO DO WAS DELETE NUCLEOTIDES FROM A YEAST GENE, SO THIS IS A YEAST TRANSFER RNA GENE, WHICH WE WANTED TO DELETE 14 OF THE BUILDING BLOCKS. AND WE USED TO DO THAT WE USED THE PROCESS OF PRIMER EXTENSION WITH OLIGONUCLEOTIDE PRIMERS AND THIS PROCESS ALLOWED US TO DELETE THOSE 14 BUILDING BLOCKS.

IN THE COURSE OF ANALYSIS OF THESE PARTICULAR BUILDING BLOCK, THESE PARTICULAR EXPERIMENTS WE USED A PROCESS CALLED

PRIMER EXTENSION. YOU'VE HEARD MUCH ABOUT IT AND BASICALLY WHAT IT WAS WAS SIMPLY A PROCEDURE, ANALYTICAL PROCESS YOU'RE NOT TO DETERMINE DNA SEQUENCE BUT SIMPLY TO ADD A PRIMER WHICH WOULD BIND TO A PARTICULAR SITE TO A DOUBLE STRANDED DNA TEMPLATE WHICH HAD BEEN DENATURED AND TO DETERMINE THE DISTANCE FROM THAT PRIMER TO THE END OF THE MOLECULE WHICH HAD BEEN PRODUCED BY ANOTHER ENZYME CALLED RESTRICTIONS ENZYME.

IF THIS DISTANCE WAS A PARTICULAR LENGTH, FOR EXAMPLE, IN THIS CASE I THINK IF IT WAS 34 NUCLEOTIDES, WE HAD NOT REMOVED THOSE SEQUENCES. IF, ON THE OTHER HAND, IT WAS 20 NUCLEOTIDES, WE HAD 14 FEWER NUCLEOTIDES OR BUILDING BLOCKS THAT WAS THE ANALYTICAL WE USED TO DETERMINE WHETHER WE WERE SUCCESSFUL IN DELETING THOSE SPECIFIC 14 NUCLEOTIDES.

Q. DOCTOR, DID YOU FIND YOU COULD SUCCESSFULLY USE THE PRIMER EXTENSION ON THIS DOUBLE STRANDED DNA FROM YEAST?

A. YES, IT WORKED WELL AS AN ANALYTICAL TOOL.

Q. DID YOU OBSERVE ANY PROBLEM AS A RESULT OF THE PENDENCY OF THE TEMPLATE STRAND TO COME BACK TOGETHER AND PREVENT THE PRIMER?

A. NO PROBLEM.

Q. I LIKE TO HAND YOU TWO OTHER ARTICLES, SCIENTIFIC ARTICLES WE'VE MARKED THESE AS EXHIBITS A . . . A-110 AND A-109.

CAN YOU IDENTIFY THESE, DOCTOR?

A. YES, THESE ARE TWO SCIENTIFIC PUBLICATIONS THAT WERE PREPARED AND PUBLISHED BY DR. HONG FROM WHEN HE WAS WORKING AT

THE M.R.C. LABORATORY IN CAMBRIDGE, ENGLAND. I BELIEVE IN THE LABORATORY OF DOCTOR FRED SANGER, THE DEVELOPER OF THE DNA SEQUENCING METHOD.

Q. WE PLACED ON THE EASEL A BLOW UP OF THE FIRST TWO PAGES OF THIS ARTICLE, CAN YOU EXPLAIN WHAT THE ARTICLE IS ABOUT?

A. THIS WAS AN ARTICLE PUBLISHED IN 1981, AS I SAID, BY DR. HONG. AND AS I ALSO SAID EARLIER DOCTOR SANGER'S LABORATORY HAD DEVELOPED A PROCEDURE FOR DETERMINING SEQUENCE OF DNA FROM BEING SINGLE STRANDED DNA TEMPLATES AND THEY WERE CIRCULAR TEMPLATES BECAUSE THEY WERE THE CHROMOSOME OF A SMALL VIRUS WHICH INFECTION BACTERIA.

THE PROBLEM WITH A SINGLE STRANDED TEMPLATE IS BECAUSE DNA HAS THIS DIRECTIONALITY WE'VE BEEN TALKING ABOUT 5 PRIME 3 PRIME VERSUS 3 PRIME 5 PRIME, IT ONLY ALLOWED YOU TO DETERMINE SEQUENCE INFORMATION IN ONE DIRECTION, SO IT WAS A RATHER

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INEFFICIENT, POTENTIALITY INEFFICIENT WAY TO DO DNA SEQUENCING.

WHAT DR. HONG WANTED TO DEMONSTRATE WAS THAT IT WAS POSSIBLE TO DETERMINE THE SEQUENCE IN THE OPPOSITE DIRECTION BY DOING FIRST A PRIMER EXTENSION REACTION WHICH COPIED THE INFORMATION FROM THE FIRST STRAND INTO A NEW STRAND AND THIS IS A SORT OF COMPLICATED FIGURE TO DEMONSTRATE THAT, BUT YOU CAN SEE THE FIRST PRIMER IS GOING -- IS IN WHITE.

SO THE FIRST PRIMER IS IN WHITE AND IT'S ADDED TO THE TEMPLATE AND A PRIMER EXTENSION REACTION IS DONE. SO WHAT YOU'VE DONE HERE IS COPIED THE INFORMATION IN THIS SINGLE

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STRANDED DNA TO FORM A NEW STRAND AND THIS PORTION IS DOUBLE STRANDED NOW.

SO THIS IS A DOUBLE STRAND DNA TEMPLATE WHICH IS GOING TO BE SUBJECTED TO SEQUENCING. YOU WANT TO READ THE INFORMATION IN THIS DIRECTION RATHER THAN IN THIS DIRECTION. IN ORDER TO ACCOMPLISH THIS DR. HONG REMOVES THE EXCESS FIRST PRIMER AS SHOWN HERE, DENATURES THE DOUBLE STRANDED PORTION TO PRODUCE THIS AND THEN PERFORMS A PRIMER EXTENSION REACTION ON THE PRODUCT OF THE FIRST CYCLE TO DO A DNA SEQUENCING DIRECTION IN THIS DIRECTION.

AND YOU CAN SEE THAT HE'S USING A DOUBLE STRANDED DNA TEMPLATE WHICH HAS BEEN DENATURED TO ACCOMPLISH A PRIMER EXTENSION REACTION WITH THE SECOND PRIMER.

Q. THERE'S BEEN CONSIDERABLE DISCUSSION OF A STATEMENT IN THE CLAIM OF THE '202 PATENT THAT THE EXTENSION PRODUCT SYNTHESIZED FROM ONE PRIMER WHEN IT IS SEPERATED FROM ITS COMPLIMENT CAN SERVE AS THE TEMPLATE FOR SYNTHESIS OF THE EXTENSION PRODUCT OF THE OTHER PRIMER. DOES THAT CONDITION EXISTS IN THE STEPS THAT DR. HONG PERFORMED HERE?

A. YES, THAT'S EXACTLY WHAT HIS GOAL WAS, WAS TO DO A PRIMER EXTENSION REACTION IN THIS DIRECTION SUCH THAT THE REGION THAT WAS GOING TO BE COMPLIMENTARY TO THE SECOND PRIMER WAS COPIED AND CAN BE USED AS THE TEMPLATE FOR THE SUBSEQUENT PRIMER EXTENSION REACTION.

Q. WHEN DID DR. HONG FIND IT NECESSARY TO REMOVE THE EXCESS OF

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THE FIRST PRIMER?

A. IT WAS NECESSARY TO REMOVE THE EXCESS OF THE FIRST PRIMER IN THIS CASE BECAUSE IF YOU DIDN'T, THEN IN THIS PARTICULAR REACTION YOU WOULD HAVE THE OTHER PRIMER PRESENT AND YOU WOULD BE GETTING SEQUENCE IN THIS DIRECTION AND SEQUENCE IN THIS DIRECTION AT THE SAME TIME THAT WOULD BE TERRIBLY CONFUSING.

Q. BUT IF, IN EFFECT, YOU HAVE TWO PRIMER EXTENSION REACTIONS GOING ON AT THE SAME TIME IN OPPOSITE DIRECTIONS ON THE DIFFERENT STRANDS, IS THAT WHAT YOU'RE TESTIFYING TO?

A. YES, IF YOU REMOVE THE FIRST PRIMER YOU WOULD HAVE GOTTEN EXTENSION FROM BOTH PRIMERS WHICH WAS ACTUALLY A PROBLEM IN HIS EXPERIMENT.

Q. THAT WOULDN'T HAVE BEEN CONSISTENT WITH WHAT DR. HONG WAS TRYING DO DO?

A. CLEARLY THE GOALS OF THIS LABORATORY WERE TO DETERMINE DNA SEQUENCE. THIS WAS ONE OF THE APPROACHES THAT THEY THOUGHT WOULD IMPROVE THE EFFICIENCY OF ACCUMULATING DATA.

YOU MUST REALIZE THE AMOUNT OF DATA THEY WANTED TO ACCUMULATE WAS ENORMOUS. THE HUMAN CHROMOSOME, FOR EXAMPLE, HAS THREE BILLION, 3,000 MILLION OF THESE BUILDING BLOCKS AND THEY WERE TARGETED MUCH SMALLER CHROMOSOMES THE CHROMOSOMES OF BACTERIAL VIRUSES, BUT THEY WERE STILL NUMBERED IN THE 50,000 BUILDING BLOCKS AN ENORMOUS TASK EVEN FOR SUCH A LABORATORY, SO PROCEDURES LIKE THIS WERE DEVELOPED TO INCREASE EFFICIENCY.

Q. IN YOUR READING OF THIS PAPER, IS IT YOUR UNDERSTANDING DR.

HONG RECOGNIZED HE NOT REMOVED THE EXCESS OF THE FIRST PRIMER BEFORE HE DID THIS NEXT STEP HE WOULD HAVE HAD EXTENSIONS GOING ON BOTH OF THE TEMPLATES AT THE SAME TIME?

A. YES, AND HE STATED THAT YOU HAD TO REMOVE THE SECOND PRIMER. THE FIRST PRIMER, EXCUSE ME.

Q. WAS DR. HONG ABLE TO CARRY OUT THIS REACTION WITHOUT EXPERIENCING ANY DIFFICULTY FROM THE TWO TEMPLATE STRANDS COMING BACK TOGETHER AND INTERFERING?

A. SINCE DR. HONG WAS SUCCESSFUL CLEARLY THE INTERFERENCE BY THE STRAND ANNEALING WAS NOT A PROBLEM.

Q. I THINK I HANDED YOU A SECOND EXHIBIT THAT WE'VE MARKED AS EXHIBIT A-110, CAN YOU IDENTIFY THAT ONE, PLEASE?

A. ACTUALLY MARKED AS A-109.

Q. 109, I'M SORRY.

A. YES, THIS IS ANOTHER PAPER BY DR. HONG PUBLISHED ABOUT A YEAR LATER --

Q. JUST FOR THE RECORD I'LL NOTE WE PUT ON THE EASEL BLOW UPS OF PAGEES 907 AND 911 FROM THIS ARTICLE.

A. AND DR. HONG WAS AWARE THAT DOUBLE STRANDED DNA TEMPLATES COULD SERVE AS TEMPLATES, OF COURSE, AFTER THE DENATURATION OF THE TWO STRANDS TO ACCOMPLISH DNA SEQUENCING.

AGAIN THEY WERE INTERESTED IN PROVING THE EFFICIENCY OF ACCUMULATING INFORMATION AND SO THIS PAPER DEALS WITH USING A WHOLE CHROMOSOME AS THE DNA TEMPLATE BEFORE DOING THE DNA SEQUENCING. THE CHROMOSOME IN THIS CASE IS 48,500 AND TWO

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BUILDING BLOCKS IN LENGTH.

OF COURSE, IN EACH OF THE TWO STRANDS THAT MANY BUILDING BLOCKS, AND HE WAS USING THE DOUBLE STRANDED DNA AS THE TEMPLATE AFTER DENATURATION FOR DNA SEQUENCING.

Q. DID DR. HONG REACH ANY CONCLUSIONS ABOUT HIS ABILITY TO USE A PRIMER EXTENSION REACTION WITH DOUBLE STRANDED DNA?

A. WELL, AS HIGHLIGHTED HERE IN SUMMARY IT CAN BE DEMONSTRATED IN THIS WORK THAT THE DNA SEQUENCE CAN BE QUICKLY AND EASILY DETERMINED BY THE DEOXY METHOD, THAT'S THE METHOD WE'VE BEEN TALKING ABOUT ON THE DOUBLE STRANDED LARGE DNA MOLECULES USING SYNTHETIC PRIMERS.

HE WAS, IN ADDITION I SHOULD SAY, HE WAS MOTIVATED TO DO THIS BECAUSE DNA SYNTHESIS ALLOWED YOU TO DESIGN YOUR PRIMERS SO THAT BY HAVING SUCH A LONG TEMPLATE YOU COULD SIMPLY DESIGN THE PRIMER TO BE WHERE YOU WANTED INFORMATION AND DO SEQUENCING IN THE VICINITY OF THAT PRIMER.

Q. DOES DR. HONG MAKE ANY COMMENTS ABOUT THE DEVELOPMENTS IN SYNTHESIS, OF ORGANIC SYNTHESIS OF DNA IN CONNECTION WITH THIS PROCESS?

A. WELL, IN THE BEGINNING OF THE PAPER HE SAYS THAT RECENT PROGRESS IN THE FIELD OF SOLID-PHASE OLIGONUCLEOTIDE SYNTHESIS. I SHOULD FIRST SAY THIS IS THE WAY DNA IS MADE IN AN AUTOMATED MACHINE. IT'S DONE IN A LITTLE COLUMN, A LITTLE PIECE, A LITTLE RESERVOIR FOR A SOLID SUPPORT.

THE DNA, THE GROWING CHAIN GROWS ON THIS SOLID SUPPORT

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THAT'S CALLED SOLID-PHASE SYNTHESIS, SOLID-PHASE OLIGONUCLEOTIDE SYNTHESIS. MEANS PRIMER SYNTHESIS IS NO LONGER A PRACTICAL LIMITATION.

HE SAYS STARTED WITH BLOCK MONITORS THAT'S THE RDT CHEMICAL BUILDING BLOCKS TO USE TO BUILD THE DNA SEQUENCE A 230 BASE OLIGONUCLEOTIDE CAN BE SYNTHESIZED AND PURIFIED IN A WEEK. SO IN 1982 YOU COULD SEE THAT PRIMER TOOK ABOUT A WEEK TO MAKE IN HIS EXPERIENCE.

Q. DR. HONG CONSIDERED THAT AN ADVANCE IN RECENT TIMES BY HIS COMMENT I GATHER?

A. YES.

Q. DOCTOR, DO YOU DRAW ANY CONCLUSIONS CONCLUSIONS FROM THESE ARTICLES WHETHER A PERSON OF ORDINARY SKILL WOULD HAVE BEEN DISCOURAGED FROM ATTEMPTING DR. KHORANA'S PROCEDURE BECAUSE OF THIS COMMENT THAT DR. KHORANA MADE ABOUT THE POSSIBILITY OF THE TEMPLATE STRANDS COMING BACK TOGETHER?

A. WELL, BECAUSE THESE PAPERS AND ACTUALLY I GUESS OTHERS SHOW THAT THIS WAS NOT A PROBLEM, I WOULD WOULDN'T HAVE CONSIDERED IT TO DISCOURAGE ONE FROM ATTEMPTING DR. KHORANA'S PROCEDURE.

Q. NOW, YOU'VE CITED ARTICLES THAT YOU WROTE AND ARTICLES THAT DR. HONG, WHO IS IN DR. SANGER'S LABORATORY WROTE, YOU DON'T CONSIDER YOURSELF AND PEOPLE IN DR. SANGER'S LABORATORY TO HAVE BEEN PEOPLE OF ORDINARY SKILL IN THE ART, DO YOU?

A. I DON'T KNOW HOW ORDINARY OR OUT OF THE ORDINARY I MIGHT BE, BUT THE CERTAINLY DR. SANGER'S OUT OF THE ORDINARY. BUT THE

POINT IS, IS THAT THIS IS THE WAY SCIENCE WORKS. YOU DO EXPERIMENTATION; YOU COME REACH CONCLUSIONS BASED ON THAT EXPERIMENTATION; THEN YOU PREPARE A PUBLICATION AND GIVE IT TO THE SCIENTIFIC COMMUNITY, SO THESE ARE AVAILABLE TO PEOPLE TO READ AND UNDERSTAND. SO THE INFORMATION WAS AVAILABLE FROM MANY LABORATORIES.

Q. DOCTOR, I'M GOING TO TURN TO A DIFFERENT SUBJECT NOW. YOU MAY RETURN TO THE WITNESS STAND.

DR. WALLACE, WE'VE HEARD SOME DISCUSSION OF SO-CALLED SECONDARY STRUCTURES OR FOLDING UP OF DNA, HAVE YOU CONSIDERED WHETHER THE POSSIBILITY OF DNA TEMPLATE FORMING SECONDARY STRUCTURES WOULD HAVE DISCOURAGED A PERSON OF ORDINARY SKILL IN 1984 FROM PRACTICING A PROCESS DESCRIBED IN THE KHORANA PRIOR ART PUBLICATION?

A. WELL, PERHAPS I SHOULD BACK UP AND EXPLAIN WHAT SECONDARY STRUCTURE IS FIRST.

Q. THAT MIGHT BE A GOOD IDEA.

A. AS YOU SEE THAT THE PRIMER CAN FIND A REGION ON THE TEMPLATE OF WHAT WE CALL COMPLIMENTARITY SO THAT THE STICKING CAN HAPPEN. IT CAN ALSO HAPPEN THAT THAT REGION OF COMPLIMENTARITY IS ACTUALLY PRESENT IN THE SAME STRAND OF DNA, SO THE STRAND CAN FOLD BACK ON ITSELF AND FORM THE SAME SORT OF DOUBLE STRANDED REGION, BUT NOW IT'S WHAT WE -- WITHIN THE SAME MOLECULE THAT'S OFTEN CALLED A HAIR PIN OR SECONDARY STRUCTURE.

I DON'T THINK THAT SECONDARY STRUCTURE GENERALLY WOULD

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HAVE DISCOURAGED ANYBODY OR THE POSSIBILITY OF IT FROM PERFORMING THE PRIMER EXTENSION REACTION AND THE AMPLIFICATION PROCESS OF DR. KHORANA BECAUSE THIS, IF THIS WERE A PROBLEM, IT WOULD HAVE BEEN A PROBLEM IN THE DNA SEQUENCING THAT I TALKED TO YOU ABOUT. AND IT WASN'T GENERALLY SEEN AS A PROBLEM, SO I DON'T THINK THAT IT WOULD HAVE BEEN CONSIDERED A -- OR DISCOURAGE ONE FROM TRYING.

Q. DID ANY OF DR. KHORANA'S PUBLICATIONS ACTUALLY ADDRESS THAT POTENTIAL SITUATION?

A. YES. WELL, DOCTOR KLEPPE'S ARTICLE ADDRESSED THAT ISSUE SPECIFICALLY. HE WAS INVESTIGATING THE REPAIR APPLICATION REACTION THAT WAS WHAT HE CALLED IT OR PRIMER EXTENSION REACTION ON TEMPLATES WHICH COULD FORM THESE KINDS OF SECONDARY STRUCTURES.

THE GENE THEY WERE WORKING WITH WAS PARTICULARLY PRONE TO THIS KIND OF SECONDARY STRUCTURE AND HE DID EXPERIMENTS IN WHICH HE VARIED PRIMER LENGTH AS A WAY AVOIDING THIS AND CAME TO THE CONCLUSION THAT IT COULD BE AVOIDED, IT WASN'T GENERALLY A PROBLEM AND THE SOLUTION GENERALLY INVOLVED USING LONGER PRIMERS.

Q. DO SOME DNA'S HAVE MORE OF A TENDENCY TO FORM THESE STRUCTURES THAN OTHERS?

A. YES, IT IS A PROPERTY OF THE PARTICULAR DNA SEQUENCE, AND SINCE NATURE CONTROLS THE SEQUENCE OF OUR GENES WE HAVE VERY LITTLE CONTROL OVER THE DEGREE OR LACK THERE OF OF WHICH A

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PARTICULAR SEQUENCE WOULD FORM THAT STRUCTURE.
Q. IS THERE ANYTHING IN THE '202 PATENT THAT WOULD TEACH SOMEONE HOW TO AVOID THESE SECONDARY STRUCTURE PROBLEMS?
A. NO, I DON'T BELIEVE THAT WAS ADDRESSED AT ALL. AS I SAID THE SECONDARY STRUCTURES ARE A PROBLEM IT'S UNDER THE CONTROL OF THE NATURAL SEQUENCE ONE IS TRYING TO AMPLIFY, SO YOU'RE MORE OR LESS STUCK WITH THE SITUATION.
Q. DR. KORNBERG WAS ASKED SOME QUESTIONS ABOUT THE RAMIFICATIONS OF A PRIMER EXTENSION REACTION NOT GOING ALL THE WAY TO THE END. HAVE YOU CONSIDERED WHETHER A SCIENTIST OF ORDINARY SKILL IN EARLY 1984 WOULD HAVE BEEN DISCOURAGED FROM PERFORMING DR. KHORANA'S REACTION BECAUSE OF THE POSSIBILITY THAT THE PRIMER EXTENSION WOULDN'T GO ALL THE WAY TO THE END?
A. WELL, I DON'T THINK SOMEBODY WOULD HAVE BEEN DISCOURAGED. PRIMER EXTENSION REACTIONS WERE, AS I SAID, DONE ROUTINELY. THE PAPER I DESCRIBED FROM MY LABORATORY IN 1980 AND THE SCIENCE PAPER IN 1980 PERFORMED A REACTION WHICH REQUIRED THE REACTION TO GO TO THE END. OTHERWISE WOULDN'T HAVE BEEN ABLE TO INCLUDE -- DRAW CONCLUSIONS FROM THE EXPERIMENT AND OTHER SUCH REACTIONS DONE IN THE OTHER LABORATORIES AND MY OWN INDICATED THAT THE REACTION WENT TO THE END. DOCTOR KLEPPE'S OWN WORK INDICATED THE REACTION WENT TO THE END.
Q. I THINK YOU MENTIONED IN CONNECTION WITH THE HONG PAPER THEY WERE RUNNING A PRIMER EXTENSION REACTION AND A SEQUENCING MODE THAT WENT MANY THOUSANDS OF BASIS OR NUCLEOTIDES, RIGHT?

A. WELL, I DON'T KNOW THEIRS WENT MANY THOUSANDS.
Q. BUT THAT WAS NOT UNCOMMON AT THE TIME?
A. DNA SEQUENCING REACTIONS OFTEN WENT IN THE HUNDREDS OF NUCLEOTIDES, BUT OTHER PRIMER EXTENSION REACTIONS, FOR EXAMPLE, CNA SYNTHESIS WHICH I MENTIONED EARLIER UNDERWENT, COULD OFTEN HAVE GONE MANY THOUSANDS OF NUCLEOTIDES.
Q. AS YOU READ THE PROCESS CLAIMED IN THE '202 PATENT, FOR EXAMPLE, FOR THE HYPOTHETICAL EXAMPLE WE WERE TALKING ABOUT, HOW LONG WOULD THE PRIMER EXTENSION HAVE TO EXTEND FOR THAT?
A. THERE'S NO EXPLICIT STATEMENT OF TEMPLATE LENGTH OR PRIMER LENGTH. IT'S A GENERAL STATEMENT OF THE PROCESS. IT DOES INDICATE THAT THE REACTION WOULD HAVE TO EXTEND FAR ENOUGH SO THAT THE PRODUCT OF THE FIRST STRAND WOULD HAVE SERVED AS A TEMPLATE FOR THE SECOND ROUND.
Q. THAT MEANS, IT WOULD HAVE TO EXTEND DOWN CLOSE TO THE END?
A. CLOSE TO THE END OR CLOSE TO THE END, YES.
Q. SO THAT COULD BE 30 OR 50 NUCLEOTIDES, FOR EXAMPLE?
A. 25, FOR EXAMPLE.
Q. DOCTOR, DR. KORNBERG TESTIFIED -- WAS ASKED SOME QUESTIONS ABOUT THE FAITHFULNESS OF DNA POLYMERASE IN COPYING A STRAND, IS IT YOUR UNDERSTANDING DNA POLYMERASE DOES INDEED MAKE SOME MISTAKES FROM TIME TO TIME?
A. YES, AND DIFFERENT DNA POLYMERASE MAKE DIFFERENT MISTAKES AT DIFFERENT FREQUENCIES.
Q. HAVE YOU CONSIDERED WHETHER A SCIENTISTS OF ORDINARY SKILL

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IN EARLY 1984 WOULD HAVE BEEN DISCOURAGED FROM ATTEMPTING DR. KHORANA'S PROCESS BECAUSE OF THIS POSSIBILITY THAT DNA POLYMERASE CAN MAKE A MISTAKE?

A. WELL, I DON'T THINK SO. WE KNEW FROM EXPERIMENTS IN WHICH WE HAD COPIED MESSENGER RNA AND INTRODUCED THEM INTO BACTERIA AND SUBSEQUENTLY DETERMINED THE SEQUENCE OF THE PRIMER EXTENSION PRODUCT THAT MISTAKES WERE INDEED RARE AND I THINK DR. KORNBERG ALSO SAID THAT THE MISTAKES WERE RARE.

SO I THINK THAT WOULD YOU HAVE TAKEN THE POSITION THAT MISTAKES WOULD BE RARE AND, SECOND OF ALL, THEY WOULD BE RANDOM, OR MORE OR LESS RANDOM. SO THAT EVEN IF MISTAKES HAD OCCURRED THEY WOULD OCCUR AT RANDOM THROUGH THE PRIMER EXTENSION PRODUCT. SO YOU WOULDN'T HAVE BEEN DISCOURAGED, I DON'T THINK.

Q. DR. WALLACE, YOU INDICATED THAT YOU ARE FAMILIAR WITH MODERN DAY PCR AND I BELIEVE YOU USE THAT TECHNIQUE IN YOUR LABORATORY?

A. YES, I AM. AND, YES, I DO.

Q. IN YOUR OPINION, IS THE KIND OF EXPERIMENTATION THAT WE TALKED ABOUT IN CONNECTION WITH THE HYPOTHETICAL REACTION IN 1984, IS THAT KIND OF EXPERIMENTATION ALSO REQUIRED TODAY WHEN SOMEONE ATTEMPTS A PCR REACTION?

A. OH, YEAH, PCR REACTIONS DON'T ALWAYS WORK. CERTAINLY DON'T OFTEN -- OFTEN DON'T WORK THE WAY YOU WANT THEM TO WORK TO ACHIEVE THE DESIRED GOAL. AND SO UNDER GOES OR DOES IN THE LABORATORY ROUTINE EXPERIMENTATION TO GET THE REACTION TO WORK BETTER, LET'S SAY.

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Q. NOW, YOU'VE READ THE '202 PATENT, DOES THE '202 PATENT DESCRIBE HOW TO SUCCESSFULLY PERFORM PCR IN EVERY SITUATION?

A. NO. AS A MATTER OF FACT, THE '202 PATENT HAS SEVERAL EXAMPLES IN IT, BUT BASICALLY THEY DEAL WITH ONE GENE WHICH IS THE HUMAN BETA GLOBIN GENE WHICH IS A GENE WHICH PRODUCES ONE OF THE COMPONENTS OF THE HEMOGLOBIN THAT'S IN OUR BODY.

THAT GENE IN DIFFERENT CIRCUMSTANCES THERE'S SEVERAL EXAMPLES DEALING WITH THAT GENE, THEN AN EXAMPLE DEALING WITH A PLASMID AS I DESCRIBED EARLIER, BUT THEY DON'T THEN DEAL WITH MANY DIFFERENT GENES WHICH MAY GIVE YOU DIFFERENT PROBLEMS AND THEY DON'T DISCUSS PROBLEMS THAT MIGHT BE ENCOUNTERED EXPLICITLY.

Q. WELL, IF SCIENTISTS OF ORDINARY SKILL RUNNING A PCR REACTION TODAY ENCOUNTERS A PROBLEM WITH THE REACTION, WHAT DOES THAT PERSON DO?

A. WELL, TODAY YOU WOULD GO TO -- YOU WOULD EITHER, FIRST OF ALL, TRY OTHER EXPERIMENTS IN YOUR LABORATORY. OR YOU MAY CONTACT A COLLEAGUE WHOSE HAD SIMILAR PROBLEMS AND SEEK ADVICE OR YOU'LL GO TO THE LITERATURE. THERE'S BEEN MANY PUBLICATIONS, THERE IS A BOOK CALLED PCR PROTOCOLS WHICH WAS PUBLISHED WHICH WAS DESIGNED TO GIVE SCIENTISTS SOME INSIGHT INTO THE PARAMETERS TO VARY IN YOUR EXPERIMENTATION.

Q. WE'VE MARKED AS EXHIBIT A-26 AN EXCERPT FROM THAT BOOK I THINK THAT YOU JUST MENTIONED, PCR PROTOCOLS; IS THAT RIGHT?

A. YES.

Q. WHEN WAS PCR PROTOCOLS PUBLISHED?
A. I BELIEVE 1989, BUT DOESN'T SAY THAT HERE, SO.
Q. NOW, ARE YOU FAMILIAR WITH IF EDITORS ON PCR PROTOCOLS?
A. I KNOW OF THEM, YES.
Q. WHO ARE THEY?
A. DOCTORS GELFAND AND SNINSKY WORK AT CETUS. DR. WHITE I BELIEVE NOW WORKS FOR HOFFMAN-LA ROCHE.
Q. WHAT DO YOU UNDERSTAND THE PURPOSE OF THIS BOOK, PCR PROTOCOLS, TO BE?
A. WELL, IT WAS TO PROVIDE A SOURCE OF HELP TO PEOPLE PRACTICING PCR. IT PROVIDED INSIGHTS INTO PROBLEMS THEY MAY BE HAVING AS WELL AS SPECIFIC APPLICATIONS THAT THEY MAY WISH TO EXPLOIT.
Q. IS THIS THE -- WE WON'T MARK THIS AS AN EXHIBIT, IS THIS THE ORIGINAL BOOK FROM WHICH THIS COPY IS MADE?
A. YES, IT IS.
Q. CAN YOU CONFORM IT WAS PUBLISHED IN 1989?
A. ACTUALLY THE COPYRIGHT IS 1990. SO PRESUMABLY IT WAS WRITTEN IN 1989.
Q. DOCTOR, WHAT KINDS OF PROBLEMS DOES PCR PROTOCOLS IDENTIFY THAT MIGHT OCCUR IF ONE IS RUNNING A PCR REACTION TODAY?
A. WELL, PROBABLY THE WORST PROBLEM IS IT DIDN'T WORK, SO YOU GOT NO PRODUCT, THAT WOULD BE ONE PROBLEM.
ANOTHER PROBLEM MIGHT HAVE BEEN IT DIDN'T WORK WELL OR IT WAS INEFFICIENT.

ANOTHER PROBLEM MIGHT HAVE BEEN IT DIDN'T WORK SPECIFICALLY, SO THAT YOU GOT MORE THAN THE GENE YOU WERE TRYING TO AMPLIFY AMPLIFIED.

ANOTHER PROBLEM IS SOMETHING CALLED PRIMER DIMMER (PHONETIC) WHICH IS THE PRIMERS INTERACT WITH EACH OTHER SO THE TEMPLATE THAT YOU GET CONSUMED IN THE REACTION.

Q. DOES THIS BOOK OFFER ANY SOLUTIONS OR ROAD MAPS FOR DEALING WITH THOSE PROBLEMS?

A. WELL, IT PROVIDES INSIGHT INTO THOSE PROBLEMS. THEN BASICALLY GUIDES ONE TO EXPERIMENT, CHANGE PRIMER LENGTHS OR POSITIONS, THAT SORT OF THING.

Q. I'D LIKE TO READ A SENTENCE FROM THE PREFACE OF THIS BOOK THAT WAS WRITTEN BY A DR. WHITE, SAYS:

"THERE IS NO SINGLE SET OF INSTRUCTIONS THAT WORKS IN EVERY SITUATION, EVEN THOUGH SOME AUTHORS HAVE DRAWN DEFINITIVE CONCLUSIONS FROM A SINGLE SYSTEM ABOUT THE IMPORTANCE OR DISPENSABILITY OF CERTAIN PARAMETERS."

DO YOU THINK THAT'S AN ACCURATE STATEMENT?

A. YEAH, I THINK THAT THERE ARE PROBLEMS WITH THE REACTION THAT CAN HAPPEN AND THAT THERE WAS NO REALLY COMPENDIUM OF INFORMATION TO DRAW ON.

Q. AND WITH REGARD TO THE STATEMENT THERE IS NO SINGLE SET OF INSTRUCTIONS, DO YOU UNDERSTAND THAT TO INCLUDE THAT THE '202 PATENT DOESN'T CONTAIN A SINGLE SET OF INSTRUCTIONS THAT WILL

ALLOW ONE TO SUCCESSFULLY USE PCR IN EVERY SITUATION?
A. I CONCLUDE THAT '202 PATENT DOES NOT INCLUDE THOSE INSTRUCTIONS. THE '202 PATENT BASICALLY DESCRIBES THE PROCESS IN GENERALITIES. IT'S A VERY BROAD CLAIM, CLAIM 1 AND IT IS FROM THAT THAT YOU REALLY UNDERSTAND YOU'RE SUPPOSE TO UNDERSTAND HOW PCR WORKS AND THE EXAMPLES REALLY, AS I SAID, REALLY RESTRICT YOU TO A FEW EXAMPLES.
Q. DOES THIS FACT THAT THE '202 PATENT DOESN'T TELL YOU HOW TO MAKE PCR WORK IN EVERY SITUATION, TELL YOU HOW MUCH CREDIT CETUS GAVE THE PERSON OF ORDINARY SKILL IN THE ART IN 1984 FOR BEING ABLE TO CONDUCT THE KIND OF EXPERIMENTATION REQUIRED?
MR. PASAHOW: OBJECTION, YOUR HONOR. CALLS FOR SPECULATION.
THE COURT: OBJECTION SUSTAINED AS TO, AT LEAST AS TO THE WAY THE QUESTION WAS PHRASED.
MR. FIGG: LET ME REPHRASE IT.
Q. DR. WALLACE, CAN YOU COMPARE THE LEVEL OF ORDINARY SKILL OR THE LEVEL OF SKILL, CAN YOU YOU COMPARE THE LEVEL OF SKILL REQUIRED TO CONDUCT THE KINDS OF EXPERIMENTS TODAY TO ADOPT THE PCR TO A NEW TECHNIQUE WITH THE LEVEL OF SKILL REQUIRED TO FOLLOW THE TEACHINGS OF DR. KHORANA'S PUBLICATIONS AND MAKE THE KIND OF HYPOTHETICAL REACTION WE DISCUSSED EARLIER WORK?
A. WELL, IT'S HARD TO COMPARE, BUT I'D SAY THEY'RE SIMILAR. OFTEN IF YOU TRY PCR REACTION IT WON'T WORK AND IT CAN TAKE YOU WEEKS OF EXPERIMENTATION TO GET IT TO WORK OPTIMALLY.

THAT WAS BASICALLY WITHIN OUR HYPOTHETICAL EXAMPLE, WE WERE TALKING ABOUT THE KHORANA PRIOR ART HOW MANY WEEKS, FIGURE IN THE ORDER OF WEEKS TO GET THAT TO WORK. SO COMPARABLE.

Q. WHAT DOES THE '202 PATENT TELL THE SKILLED PERSON IN 1984 ABOUT THE TEMPLATE CONCENTRATIONS, CONCENTRATION OF THE DNA TO USE?

A. THE PATENT USES WIDELY DIFFERENT TEMPLATE CONCENTRATIONS AND THERE'S NO EXPLICIT STATEMENT OF RECOMMENDED TEMPLATE CONCENTRATIONS IN THE CLAIMS.

Q. SO HOW WOULD ONE DETERMINE THE TEMPLATE CONCENTRATION TO USE FROM THE '202 PATENT?

A. THROUGH EXPERIMENTATION, I GUESS.

Q. WHAT DOES THE '202 PATENT SAY ABOUT THINGS LIKE HOW LONG YOU SHOULD ALLOW THE PRIMERS TO STICK TO THE TEMPLATES AND THE CONDITIONS FOR THAT STICKING?

A. THERE ARE EXAMPLES IN WHICH I DON'T REMEMBER THE EXACT CONDITIONS THAT THEY USED, BUT THEY WERE STANDARD CONDITIONS I WOULD SAY.

Q. DOCTOR, DO YOU HAVE THE '202 PATENT UP THERE STILL?

A. SOMEWHERE.

Q. I THINK IT WAS THE SECOND THING I HANDED YOU.

A. YEAH.

Q. WITH REFERENCE TO THE DISCLOSURE PART OF THIS PATENT COLUMN SEVEN, LINES 55 THROUGH 68, WHAT DOES THE PATENT TELL ABOUT THE CONDITIONS THAT THE READER SHOULD USE FOR PERFORMING THE PRIMER

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EXTENSION PART OF THE REACTION?

A. WELL, THE PATENT SAYS THAT AFTER HAVING GONE THROUGH THE DENATURATION STEP REACTION, THEN ASSEMBLED ESSENTIALLY.

"TO THE COOLED MIXTURE IS ADDED AN APPROPRIATE AGENT FOR INDUCING OR CATALYZING THE PRIMER EXTENSION REACTION, AND THE REACTION IS ALLOWED TO OCCUR UNDER CONDITIONS KNOWN IN THE ART."

SO PRESUMABLY THEY'RE SAYING THAT THAT PART OF THE REACTION IS UNDERSTOOD FROM PREVIOUS WORK IN THE ART IN THE FIELD.

Q. "KNOWN IN THE ART" WHICH MEANS?

A. GENERALLY IN THE FIELD THAT WE'RE DEALING WITH. AS I SAID PRIMER EXTENSIONS WERE WELL-KNOWN, SO CONFIRMS THAT, I GUESS.

Q. DOCTOR, WITH RESPECT TO THE LENGTHS OF THE PRIMERS TO BE USED IN THE REACTION, THERE'S SOME DISCUSSION OF THAT AT COLUMN FOUR, LINES 38 THROUGH 50 OF THE PATENT, WHAT DOES THE PATENT TEACH IN THAT REGARD?

A. WELL, BASICALLY IT'S SAYING THAT PRIMERS OF -- SHORT PRIMERS CAN BE USED. I THINK THEY SAY:

"DEPENDING ON THE COMPLEXITY OF THE TARGET SEQUENCE, THE OLIGONUCLEOTIDE PRIMER TYPICALLY CONTAINS 15 TO 25 OR MORE NUCLEOTIDES, ALTHOUGH IT MAY CONTAIN FEWER NUCLEOTIDES. FOR OTHER APPLICATIONS, THE OLIGONUCLEOTIDE PRIMER IS TYPICALLY SHORTER, FOR EXAMPLE, 7 TO 15 NUCLEOTIDES."

AND THERE ARE EXAMPLES OF THE BODY OF THE PATENT USING

PRIMERS AS SHORT AS, I THINK, AS 11 AND THEN MUCH LONGER PRIMERS.

SO THEY'RE BASICALLY SAYING YOU CAN USE PRIMERS AS SHORT AS 7 AND AS LONG AS 25 OR MORE. DOESN'T REALLY GIVE YOU ANY GUIDANCE AS TO WHAT YOU SHOULD USE FOR PARTICULAR TEMPLATE. I GUESS YOU'RE SUPPOSED TO DETERMINE THAT THROUGH EITHER EXPERIMENTATION OR PRIOR KNOWLEDGE.

Q. AND DO YOU RECALL WHAT THE KLEPPE PAPER SAID ABOUT THE LENGTHS OF THE PRIMERS THAT SHOULD BE USED?

A. WELL, AGAIN, KLEPPE PAPER CONCLUDED THAT PRIMERS AS SHORT AS -- I DON'T REMEMBER THE EXACT NUMBER, BUT 7 I THINK OR SOMETHING LIKE THAT, BUT THEN SAID THAT IF THERE WAS A POSSIBILITY THAT SECONDARY STRUCTURE WAS A PROBLEM, THEY CONCLUDED THAT THE MINIMUM LENGTH OF A PRIMER SHOULD BE ABOUT 21, I BELIEVE IT WAS. SO IN THE SAME RANGE AS DESCRIBED HERE IN THIS DOCUMENT.

MR. FIGG: YOUR HONOR, I'M ABOUT TO EMBARK ON A KNEW SUBJECT, IS THIS A GENERAL TIME FOR A BREAK?

THE COURT: I GUESS IT'S GETTING TO BE ABOUT THAT HOUR. THIS WILL BE THE SECOND AND LAST MORNING BREAK.

PUTTING YOU TO THE TEST IN FRONT OF THE JURY, HOW MUCH LONGER DO YOU THINK YOU'LL BE WITH DR. WALLACE?

MR. FIGG: IT'S GOING TO BE CLOSE WHETHER WE FINISH TODAY OR NOT. EITHER TODAY OR EARLY TOMORROW.

THE COURT: WELL, WE BETTER TAKE A RECESS, WE'RE CLOSER

TO THE END THAN THAT. WE'LL TAKE ABOUT 10 OR 15 MINUTES, LADIES AND GENTLEMEN. PLEASE FOLLOW THE INSTRUCTIONS I'VE GIVEN YOU ABOUT NOT DISCUSSING THE CASE AMONG YOURSELVES OR ANYONE ELSE. WE'LL SEE YOU AT THE CLOSE OF THE RECESS. YOU MAY STEP DOWN.

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

MR. FIGG: YOUR HONOR, THERE'S ONE AREA THAT I WAS PLANNING TO GO INTO WITH DR. WALLACE, AND I'M NOT SURE HOW AN EARLIER RULING OF YOUR HONOR'S MIGHT APPLY TO THAT OR RELATE TO THAT, SO I WANTED TO BRING THAT UP OUTSIDE OF THE HEARING OF THE JURY.

I WAS PREPARED TO ASK DR. WALLACE SOME QUESTIONS ABOUT THE PROSECUTION HISTORY OF THE '202 PATENT AND WHETHER HE DRAWS ANY CONCLUSIONS FROM THAT PROSECUTION HISTORY AS TO WHAT THE PATENTEES CONSIDERED THE LEVEL OF ORDINARY SKILL IN THE ART TO BE.

AND DR. WALLACE IN RESPONDING TO THAT QUESTION WOULD EXPLAIN THE AFFIDAVIT THAT DOCTOR ERLICH FILED IN THE PATENT AND TRADEMARK OFFICE AND THE ARGUMENTS THAT DOCTOR ERLICH MADE WITH RESPECT TO THE ABILITY OF A SKILLED PERSON TO WORK OUT THE THINGS LIKE PRIMER LENGTHS AND ANNEALING CONDITIONS AND TIMES AND SO FORTH WITH RESPECT TO THE SPECIFIC EMBODIMENT OF CLAIM 1 THAT'S REFLECTED IN CLAIM 14.

NOW, I HAD ATTEMPTED TO HAVE MR. DE GRANDI EXPLAIN JUST FROM A LEGAL STANDPOINT WHAT WAS GOING ON THERE; IN OTHER WORDS, WHAT AN AFFIDAVIT IS, WHAT THE REJECTION WAS AND SO FORTH, AND

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YOUR HONOR WAS NOT PREPARED TO ALLOW THAT TESTIMONY TO COME IN.

BUT I THINK FROM A TECHNICAL STANDPOINT THERE IS SIMPLY ADDITIONAL EVIDENCE WHAT THE LEVEL OF THE ORDINARY SKILL WAS AND WHAT THE CAPABILITY OF SUCH A PERSON WITH RESPECT TO WORK OUT SOME OF THE VERY KINDS OF CONDITIONS THAT ARE REQUIRED TO MAKE CLAIM 1 WORK.

THE COURT: DO YOU WANT TO BE HEARD ON THIS?

MR. PASAHOW: JUST BRIEFLY, YOUR HONOR.

IT'S AN ARGUMENT YOU ALREADY HEARD FROM MR. LEWIS, BUT IT GOES TO CLAIM 14, A CLAIM THAT'S NOT INVOLVED IN THE CASE AND THIS PURPORTED COMPARISON OF THE AMOUNT OF ENABLEMENT THAT WOULD BE REQUIRED IN ORDER TO MAKE CLAIM 14 A VALID CLAIM AND SOMEHOW COMPARING THAT TO THE LEVEL OF SKILL IN THE ART THAT ONE WOULD HAVE USED IN FOLLOWING THE KLEPPE ARTICLE IN ORDER TO DECIDE WHETHER OR NOT THAT ANTICIPATES OR MAKES OBVIOUS CLAIM 1, AND FOR THE REASONS YOUR HONOR EXCLUDED IT BEFORE WE THINK IT SHOULD BE EXCLUDED HERE.

MR. FIGG: YOUR HONOR, IF I MIGHT JUST POINT OUT. CLAIM 14 IS A DEPENDENT CLAIM. IT'S DEPENDENT ON CLAIM 1. SO EVERYTHING IN CLAIM 14 IS, BY DEFINITION, ENCOMPASSED WITHIN THE SCOPE OF CLAIM 1.

AND SO IN THAT REGARD THE ENABLEMENT -- THE PATENTEES' POSITIONS ON WHAT A PERSON OF ORDINARY SKILL COULD DO WITH RESPECT TO WORK OUT THE VARIOUS CONDITIONS FOR MAKING THE REACTION WORK IS HIGHLY PERTINENT TO WHAT A PERSON OF ORDINARY

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SKILL IN THE ART WOULD HAVE BEEN ABLE TO DO WITH THE KHORANA PRIOR ART.

WE'RE ALL TRYING TO GET A GRASP ON WHO THIS HYPOTHETICAL PERSON OF ORDINARY SKILL IS AND WHAT THAT PERSON MIGHT OR MIGHT NOT BE ABLE TO DO IN 1984. THIS IS SIMPLY ADDITIONAL EVIDENCE.

THE COURT: DOES DOCTOR ERLICH'S AFFIDAVIT GO TO WHAT A PERSON OF ORDINARY SKILL IN THE ART COULD ACCOMPLISH IN THAT FIELD AT THAT TIME?

MR. FIGG: IT CERTAINLY DOES, YOUR HONOR. THE VERY HEART OF THE REJECTION THAT THE EXAMINER MADE WAS THAT CLAIM 14 COVERS A CERTAIN EMBODIMENT OF CLAIM 1 AND THERE WERE NO EXPERIMENTAL DETAILS PROVIDED IN THE SPECIFICATION OF THE '202 PATENT ON HOW TO CARRY THAT OUT, AND THE EXAMINER RAISED A QUESTION, HAVE YOU REALLY TAUGHT HOW TO DO THAT.

SO CETUS ARGUED, YES, WE HAVE TAUGHT HOW TO DO IT BECAUSE A PERSON OF ORDINARY SKILL IN THE ART WOULD BE ABLE TO WORK OUT THOSE CONDITIONS WITHOUT UNDUE EXPERIMENTATION. AND CETUS PRESENTED DOCTOR ERLICH'S AFFIDAVIT AND IN THAT AFFIDAVIT DOCTOR ERLICH DESCRIBED EXPERIMENTS WHERE THEY EXPERIMENTED FOR A TIME AND FIGURED OUT HOW LONG THE PRIMERS WERE TO BE.

THEY EXPERIMENTED FOR A TIME AND THEY FIGURED THE TEMPLATES, THEY EXPERIMENT AND DETERMINED HOW LONG YOU INCUBATE THE REACTION TO MAKE IT WORK. ALL THE THINGS WE'RE TALKING ABOUT WERE ADDRESSED AND THE CONCLUSION THAT DOCTOR ERLICH

REACHED AND THE CETUS PATENT ATTORNEY REACHED WAS THAT A PERSON OF ORDINARY SKILL IN THE ART WITH ROUTINE EXPERIMENTATION, NO UNDUE EXPERIMENTATION WOULD HAVE BEEN ABLE TO WORK ALL THESE THINGS OUT. WE'RE SIMPLY SAYING THE SAME IS TRUE OF THE KHORANA PRIOR ART AND THIS IS HIGHLY PROBATIVE OF THAT.

THE COURT: YES.

MR. PASAHOW: YOUR HONOR, THAT ISN'T QUITE WHAT THE ISSUE WAS AS TO WHICH THE DECLARATION WAS FILED NOR IS IT QUITE WHAT IT SAYS.

THE ISSUE IS TO WHICH IT WAS -- HE FILED HAD TO DO WITH CLAIM 14, WHICH IS A CLAIM THAT DESCRIBES PECULIAR EMBODIMENT OF PCR WHICH USES BOTH THE THERMAL STABLE ENZYME THAT IS ONE UNLIKE THE ENZYMES WE'RE TALKING ABOUT WHICH IS NOT DESTROYED BY HEAT AND ALSO IS NOT CYCLED, THAT IS IT DOESN'T GO-BETWEEN WARMER AND COOLER TEMPERATURES.

THE QUESTION THE EXAMINER RAISED WAS THIS: AT THE TIME THE PATENT WAS APPLIED FOR THERE WAS NO THERMOSTABLE ENZYME EXPERIMENT THAT HAD BEEN DONE BECAUSE WHILE CETUS IN THE PATENT IDENTIFIED LIKELY CANDIDATE THERMOSTABLE ENZYMES KNOWN AS OF THAT TIME HAD BEEN PURIFIED AND USED IN A PCR REACTION.

WITH THAT QUESTION ASKED, CETUS PRESENTED THE EXAMINER WITH WORK IN WHICH A SCIENTIST IN A LABORATORY WORKING UNDER DR. MULLIS THE INVENTORS DIRECTION WAS ABLE TO DO THE EXPERIMENT, THAT IS COVERED BY THE CLAIM AFTER THE THERMOSTABLE ENZYME WAS PURIFIED. AND THAT WAS THE ISSUE AND THAT'S WHAT DR. ERLICH

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PRESENTED.

SO IT GOES TO A SUBSTANTIAL BODY OF WORK WHICH IS OUTSIDE WHAT'S INVOLVED IN THE CASE. AND THAT IS THE QUESTION OF THE IDENTIFICATION AND USE OF THE THERMOSTABLE ENZYME AND THAT IT GOES TO WHAT ONE WORKING UNDER THE INVENTORS DIRECTION WOULD DO BASED UPON THE PATENT, NOT WHAT ONE WHO HASN'T SEEN THIS PARTICULAR PATENT AND DOESN'T KNOW WHAT IT SAYS MIGHT BE ABLE TO DO.

IT'S ALSO A SUBJECT AS TO WHICH OBVIOUSLY OTHER WITNESSES WILL TESTIFY IF WE GET INTO IT, INCLUDING DOCTOR ERLICH.

MR. FIGG: YOUR HONOR, MR. PASAHOW HAS REALLY MISUNDERSTOOD THIS ASPECT OF PATENT PRACTICE AND WHAT THIS SUBMISSION MEANT IN RESPONSE TO REJECTION FOR LACK OF ENABLEMENT.

IT'S TRUE DOCTOR ERLICH REFERRED TO WHAT DOCTOR MULLIS COULD DO, BUT IN DOING THAT THE CONTENTION WAS THAT SINCE DR. MULLIS AND HIS TECHNICIAN DOCTOR FALOONA COULD DO IT, IT PROVED THAT A PERSON OF ORDINARY SKILL IN THE ART WAS CAPABLE WITH ROUTINE EXPERIMENTATION OF WORKING THESE THINGS OUT.

I'M RATHER SURPRISED TO HEAR MR. PASAHOW SAY THERMOSTABLE ENZYMES ARE NOT PART OF THIS CASE BECAUSE WHAT THEY ARE PLANNING TO DO IS SUBMIT EVIDENCE OF COMMERCIAL SUCCESS WITH THERMOSTABLE ENZYMES.

CLAIM 1 DOES NOT EXCLUDE THE USE OF A THERMOSTABLE

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ENZYME AND THERE WAS MUCH MORE THAN A THERMOSTABLE ENZYME INVOLVED IN THIS. THERE WAS THE TEMPERATURE USED, THE LENGTHS OF THE TEMPLATES, THE LENGTHS OF THE PRIMERS, THE THINGS I'VE ALREADY TOLD YOU ABOUT.

I CAN'T -- IT'S DIFFICULT TO IMAGINE ANYMORE PROBATIVE INFORMATION ON WHAT THE LEVEL OF ORDINARY SKILL AND THE CAPABILITIES OF A PERSON OF ORDINARY SKILL IN 1984 WERE BECAUSE THAT WAS PRECISELY THE POINT THE EXAMINER WAS RAISING, WAS THIS CLAIM WHICH IS EMBODIMENT OF CLAIM 1, DEPENDENT ON CLAIM 1, ENABLED BY THE SPECIFICATION. CETUS SAID, YES. ALL THEY HAVE TO DO IS ENOUGH EXPERIMENTATION, IT'S ROUTINE THEY CAN MAKE IT WORK.

THE COURT: WELL, THERE IS A LIMITED WAY, PERHAPS IT'S NOT REALLY THAT LIMITED, I THINK IN WHICH YOU CAN GET INTO AND EXAMINE THIS WITNESS ON DOCTOR ERLICH'S AFFIDAVIT, BUT I WANT YOU TO STAY AWAY FROM WHAT THE PATENT OFFICE, THE EXAMINER MAY HAVE CONCLUDED OR WHAT ERRORS, IF ANY, MAY HAVE BEEN MADE OR LED INTO OR ANYTHING OF THAT NATURE.

AND NUMBER 2, THE ISSUE OF ENABLEMENT WITH RESPECT TO THIS PATENT WAS NOT PUT IN ISSUE. THAT'S ONE OF THE PROBLEMS WE'VE BEEN DEALING WITH. THERE WAS AN ATTEMPT BELATEDLY TO RAISE IT.

ADMITTEDLY, THOUGH, WHAT A PERSON SKILLED IN THE ART COULD DO AT THAT TIME WITH RESPECT TO THE INFORMATION THAT WAS ALREADY AVAILABLE TO SUCH A PERSON, WHETHER KHORANA PRIOR ART,

OTHER INFORMATION AVAILABLE TO SUCH A SCIENTIST, CERTAINLY IS RELEVANT.

SO YOU MAY INQUIRE INTO THE ERLICH AFFIDAVIT FOR THE PURPOSES OF GETTING INTO THAT AREA, BUT NOT WITH RESPECT TO THE ENABLEMENT ON THE '202.

NOW, THAT'S ADMITTEDLY A FINE LINE, BUT I THINK I HAVE TO DRAW THAT BECAUSE OTHERWISE I'M ALLOWING YOU TO GET INTO AN ISSUE THAT WASN'T PROPERLY RAISED IN ADVANCE.

MR. FIGG: I THINK I UNDERSTAND YOUR HONOR'S RULE ON THIS AND WE HAVE NO INTENTION OF CHALLENGING CLAIM 14 OR AT THIS TIME ANY OTHER CLAIM FOR LACK OF ENABLEMENT.

THE COURT: OR THE ISSUE OF ENABLEMENT GENERALLY WHICH THERE WAS AN ATTEMPT TO RAISE BELATEDLY THIS CASE WAS PLED AND PROCEEDED TO TRIAL ON THE ANTICIPATION.

MR. FIGG: I UNDERSTAND YOUR HONOR'S RULING ON THAT AND OUR POINT HERE IS NOT TO CHALLENGE THE VALIDITY TO THE CLAIMS ON LACK OF ENABLEMENT, IT'S TO POINT TO THE ARGUMENTS MADE IN SUPPORT OF ENABLEMENT AS EVIDENCE OF WHAT A PERSON OF ORDINARY SKILL CAN DO.

THE COURT: AND NOT HOW PATENT EXAMINER MAY HAVE BEEN MISLED OR WHATEVER ELSE, BUT WHAT DOCTOR ERLICH SAID IN HIS AFFIDAVIT THAT MIGHT SHED LIGHT ON THE ISSUES I'VE JUST OUT LINED.

MR. FIGG: I'VE THINK WE WILL SIMPLY HAVE TO EXPLAIN THE EXAMINER DID REJECT THIS CLAIM ON THAT BASIS THEN GO INTO

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WHAT CETUS DID TO OVERCOME THAT REJECTION, AND NOT DRAW ANY CONCLUSIONS OR ILLICIT ANY TESTIMONY AT ALL ON WHETHER THE EXAMINER WAS RIGHT OR WRONG.

THE COURT: CORRECT.

MR. FIGG: OKAY.

THE COURT: I THINK WE'LL JUST HAVE TO WAIT AN AD HOC BASIS FOR THE OBJECTIONS AND DEAL WITH THEM AT THAT TIME.

ON ANOTHER MATTER, WERE YOU ABLE TO COME UP WITH A STIPULATION TO ANSWER THE JURORS QUESTIONS ABOUT THE OVERLAP?

MR. FIGG: I APOLOGIZE, YOUR HONOR, WE HAVE NOT DONE THAT YET. IN VIEW OF YOUR HONOR'S PRODING, I THINK WE WILL AGREE TO DO IT THIS AFTERNOON AND HAVE SOMETHING FOR YOU ON THAT TOMORROW.

THE COURT: YOU MAY HAVE TIME TOMORROW. ABOUT TOMORROW, I CHECKED WITH THE MARSHAL'S OFFICE AND I'M ADVISED THAT THEY ARE GUARANTEEING NO ONE ACCESS TO THE BUILDING AFTER 6:00 O'CLOCK.

MR. FIGG: IN THE MORNING?

THE COURT: IN THE MORNING. WHICH MEANS, IT'S EITHER UP AND EARLY OR STAY OVERNIGHT. I WAS TRYING TO FIGURE OUT WHICH ONE OF THOSE OPTIONS IS THE MOST VIABLE.

I DON'T -- THEY DO BELIEVE BASED UPON INFORMATION THAT THEY RECEIVED, HOW RELIABLE IT IS I DON'T KNOW, THAT THIS ASSEMBLAGE WILL MOVE ELSEWHERE ABOUT 11:30 OR 12:00 O'CLOCK AND THEY WILL BE ABLE TO PROVIDE ACCESS TO THE BUILDING AT THAT

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TIME.

I'M NOT SURE HOW HELPFUL THAT REALLY IS. MAYBE IT'S POSSIBLE TO FINISH UP THEN WITH DR. WALLACE TESTIMONY, DEPENDING ON WHAT THE JURORS CAN DO, BUT IT WOULD MEAN COMING IN HERE PROBABLY AT THE EARLIEST 12 O'CLOCK AND GIVEN THE CEREMONIES TOMORROW AFTERNOON RECESSING BY ABOUT 3:30.

IF YOU WANT TO PROCEED IN THAT FASHION, THAT'S FINE WITH ME, PRESUMABLY I'LL BE HERE. IF I CAN GET IN THE REST OF US CAN GET IN AND THEN WE'LL JUST GO THROUGH UNTIL 3:30.

MR. FIGG: DO YOU KNOW IF THEY'RE EXPECTING THIS TO END TOMORROW? HAS THERE BEEN ANY INFORMATION ON THAT?

THE COURT: IT'S NICE TO NOTIFY THEM OF THE BEGINNING AND THE END. APPARENTLY THE INFORMATION THEY HAVE 11:30 OR 12:00 O'CLOCK THEY'RE GOING TO MOVE TO SOME OTHER LOCATION, I GUESS TO THE UN PLAZA OR SOMETHING, AND THEY HAVE NO INFORMATION ABOUT THEREAFTER.

I WOULD IMAGINE THAT THERE MAY BE SPORADIC KINDS OF THINGS, NOT ON THIS MASSIVE SCALE, I JUST HAVE NO WAY OF KNOWING. SO SORT OF DAY-TO-DAY. BUT IF YOU WANT TO TALK ABOUT IT IN THE RECESS AND LET ME KNOW BEFORE I TALK TO THE JURY WHEN THEY COME BACK IN, THEN I CAN CHECK AND SEE IF THE JURORS CAN IN FACT ARRANGE THEIR SCHEDULES TO CONVENE FOR THAT PERIOD OF TIME. THEY MAY, YOU KNOW, BY NOT BEING ABLE TO.

MR. FIGG: WE'LL DO THAT.

MR. PASAHOW: YES, YOUR HONOR.

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THE COURT: OKAY.

(RECESS TAKEN AT 11:40 A.M.)

(CONTINUED ON NEXT PAGE - NOTHING OMITTED)

(OPEN COURT, JURY NOT PRESENT, AT 11:57 A.M.:)

THE COURT: WHAT DID YOU DECIDE? YOU WANTED TO COME IN AT 1:00? IS THAT WHAT YOU'RE PROPOSING?

MR. PASAHOW: WELL, YOUR HONOR, I THINK WE HAVE SLIGHTLY DIFFERENT VIEWS. WE ARE AGREED WE DON'T WANT TO CUT IT VERY CLOSE TO THE CROWD --

THE COURT: UH-HUH.

MR. PASAHOW: -- SO WE PROBABLY SHOULDN'T BE TRYING TO ARRANGE TO HAVE ALL THE NECESSARY PEOPLE HERE, WE THINK, BEFORE 1:00. IT SEEMS TO ME THAT THE INCONVENIENCE FACTOR FOR THE JURY THEN GROWS ENORMOUSLY IF IT'S JUST FOR THOSE FEW HOURS, AND WE OUGHT NOT TO TRY AND DO IT.

MR. FIGG, I THINK, HAS A SLIGHTLY DIFFERENT VIEW ABOUT WHAT WE DO AFTER 1:00.

MR. FIGG: YEAH. WELL, MY VIEW IS, WE CERTAINLY SHOULDN'T TRY TO CUT IT TOO CLOSE TO WHEN THIS CROWD -- WE DON'T KNOW HOW LARGE IT MIGHT BE -- IS BREAKING UP. THEY'RE GOING TO HAVE LOGISTICAL PROBLEMS OF CLEARING OUT, AND THE POLICE MIGHT HAVE SOMETHING TO SAY ABOUT HOW FAST THEY CLEAR OUT.

SO WHAT I WAS GOING TO SUGGEST --

THE COURT: WELL, ONE OF THE PROBLEMS IS, THERE'S GOING TO BE VERY LITTLE POLICE PROTECTION OUT THERE. THAT'S REALLY ONE OF THE PROBLEMS, SO . . .

THE OTHER THING IS, THERE'S NO ASSURANCE THAT EVERYONE WILL JOIN THE GROUP. MOBS TEND NOT TO NECESSARILY BE RULY;

RIGHT?

MR. PASAHOW: BUT, OBVIOUSLY, IF WE ARE ONE JUROR SHORT, ALL THE EFFORT WILL HAVE BEEN WASTED. THAT IS MY CONCERN.

THE COURT: WELL, IT WOULD ALL HAVE TO -- YOU KNOW, ESSENTIALLY HAVE TO BE, YOU KNOW, NOT A PHYSICAL IMPOSSIBILITY OR DIFFICULTY FOR ANY OF THEM. AND IF THERE'S A PROBLEM WITH GETTING THEM IN THE BUILDING, WE CAN PROBABLY WORK SOMETHING OUT WITH THE MARSHAL'S OFFICE, ASSUMING THAT A MAJORITY OF THE CROWD HAS DISPERSED.

IF THEY CAN DO IT, DO YOU WANT TO TRY, SAY, AT 12:30 OR 1:00? THAT, AT LEAST, WOULD GIVE -- AS I SAY, WE'RE GOING TO HAVE TO RECESS AT 3:30 BECAUSE OF THE OTHER PROCEEDING.

MR. FIGG: (NODDING HEAD.)

THE COURT: YOU WANT TO TRY TO DO IT, SAY, 12:30 -- IF I TELL THEM 12:30 AND SEE IF . . .

MR. FIGG: YES, YOUR HONOR. WE WOULD TRY THAT.

MR. PASAHOW: WELL, MY CONCERN ABOUT 12:30, YOUR HONOR, IS, ESSENTIALLY, WE -- WE WOULD ALL HAVE TO BE STARTING TO TRY AND GET INTO THE BUILDING AROUND 12:00 --

THE COURT: OH, I SEE, FOR YOUR PURPOSES.

MR. PASAHOW: -- TO DO THAT. IT TAKES US ABOUT THAT HALF HOUR. SO THAT'S WHY I WAS --

THE COURT: WELL, YOU CAN LEAVE ALL OF YOUR MATERIALS HERE. I MEAN, YOU KNOW, IN TERMS -- YOUR PROPS AND SO FORTH.

YOU . . . YOU DON'T HAVE THAT LARGE AN ENTOURAGE; DO YOU? I MEAN, WHAT HAPPENS? YOU HAVE OTHER THINGS TO BRING IN, TRANSPORT IN?

MR. PASAHOW: NOT HUGE AMOUNTS, YOUR HONOR, BUT IT TENDS TO TAKE US ABOUT 15 MINUTES TO GET THINGS ARRANGED IN THE MORNING, AND I WAS THINKING, AT LEAST OUR CURRENT PLAN IS, WE ALWAYS TRY TO LEAVE OURSELVES HALF AN HOUR TO MAKE SURE WE'RE READY TO GO ON TIME.

THE COURT: UH-HUH.

MR. PASAHOW: I EXPECT THAT THAT IS ABOUT WHAT IT TAKES.

MR. FIGG: YEAH.

THE COURT: WELL, ONE POSSIBILITY I WAS THINKING ABOUT IS TO MAYBE ASK THE JURORS TO CONVENE OVER AT THE OPERA PLAZA OR SOMEWHERE, AND THEN, YOU KNOW, EITHER SEND A COURT PERSONNEL OVER, OR IF, YOU KNOW, THERE ARE STILL LINGERING PEOPLE AROUND, SEND SOMEONE FROM THE MARSHAL'S OFFICE OVER WITH A VAN TO PICK THEM UP AND BRING THEM IN THE BUILDING SO THERE'S NO PROBLEM. AND THE REST OF YOU WILL HAVE TO FEND FOR YOURSELVES. I ONLY TAKE CARE OF THE JURORS.

(LAUGHTER)

THE COURT: I DON'T KNOW. IF YOU WALK AROUND WITH A PLACARD -- THIS CAN BE OFF THE RECORD.

(DISCUSSION HELD OFF THE RECORD)

(CONTINUED ON NEXT PAGE - NOTHING OMITTED)

(OPEN COURT, JURY PRESENT:)

THE COURT: YOU MAY RESUME THE STAND.

LADIES AND GENTLEMEN, I'VE JUST HAD A DISCUSSION WITH COUNSEL ABOUT OUR CONVENING TOMORROW AND THE DIFFICULTIES OF IT, BECAUSE THERE IS A LARGE DEMONSTRATION PLANNED OUTSIDE THE BUILDING, AND FROM PAST EXPERIENCE, IT SOMETIMES IS IMPOSSIBLE TO GET INTO THE BUILDING. IN FACT, THAT IS THE OPERATIVE FOR THE GROUP THAT IS DEMONSTRATING TOMORROW.

AND THE MARSHAL'S OFFICE HAS ADVISED US THAT THEY WILL NOT ASSIST ANYONE GETTING IN THE BUILDING AFTER 6:00 O'CLOCK IN THE MORNING. I DON'T INTEND TO HAVE YOU ALL COME IN BEFORE THAT, AND THE GROUP IS SUPPOSEDLY BREAKING UP AT AROUND 11:30, 12:00 O'CLOCK, AND GOING ELSEWHERE, AND THE MARSHALS WILL THEN OPEN THE BUILDING, OR BEFORE THAT, AT LEAST, YOU KNOW, IF YOU CAN GET IN, FINE.

SO WE CANNOT CONVENE TOMORROW MORNING, AND I TALKED TO COUNSEL ABOUT THAT, AND, OF COURSE, WE WANT TO ALSO FINISH THIS TRIAL.

SO ONE OF THE THINGS WE DISCUSSED THAT WE'D LIKE TO DO, IF IT'S CONVENIENT WITH YOU, IS TO HAVE YOU REPORT AT 12:30. WE WON'T GET IN MUCH OF A DAY, BUT GO FROM 12:30 TO 3:30. AND THE REASON WE CAN ONLY GO TO 3:30 IS BECAUSE THE COURT HAS A CEREMONIAL EN BANC SESSION TOMORROW SWEARING IN ONE OF THE NEW JUDGES, SO WE CANNOT MEET BEYOND THAT TIME.

CAN ALL OF YOU COME IN TOMORROW AT THAT TIME?

THE JURORS: (NODDING HEAD.)

THE COURT: CAN YOU ARRANGE THAT?

THE JURORS: (NODDING HEAD.)

THE COURT: OKAY. WHAT I'M GOING TO ASK YOU TO DO IS AS FOLLOWS, BECAUSE I DON'T KNOW WHAT THE SITUATION WILL BE. THEY MAY, IN FACT, NOT BREAK UP AS PLANNED OR SOME MAY STAY BEHIND OR WHATEVER, AND I DON'T WANT YOU TO BE IN HARM'S WAY.

YOU KNOW WHERE OPERA PLAZA IS?

(PAUSE IN PROCEEDINGS)

THE COURT: IT'S OVER ON VAN NESS. IT'S THE APARTMENT HOUSE -- THE APARTMENT COMPLEX WITH THE BOOK STORE AND MAX'S OPERA CAFE. IT'S ON VAN NESS RUNNING THE BLOCK BETWEEN TURK AND GOLDEN GATE.

AND ON THE VAN NESS SIDE OF IT, THERE IS AN OPEN AREA BETWEEN THE VARIOUS RESTAURANTS, A WATERFALL AND WHATEVER ELSE. IF YOU WOULD MEET THERE AT 12:30, AND THEN IF EVERYTHING IS ALL RIGHT, IF THERE ARE NO PROBLEMS HERE, AND ACCESS IS READILY AVAILABLE, THEN ONE OF THE COURT PERSONNEL WILL GO OVER TO LET YOU KNOW AND HAVE YOU COME ON OVER.

IF THERE ARE STILL SOME STRAGGLERS OR A PROBLEM, THEN I WILL HAVE SOMEONE FROM THE MARSHAL'S OFFICE COME WITH A VAN AND PICK YOU UP AND BRING YOU IN THROUGH THE BASEMENT.

ALSO, JUST IN CASE THE INSTRUCTIONS OR INFORMATION THAT WE GET CHANGE, WOULD YOU CALL THE NUMBER THAT YOU HAVE FOR THE JURY --

OR WOULD YOU PREFER THAT THEY CALL YOU, LURLINE? YOU MAY NOT GET IN HERE, EITHER.

THE CLERK: I'LL BE IN HERE. DON'T WORRY.

THE COURT: SHE'LL BE IN HERE. SHE'LL BE STAYING OVERNIGHT.

YOU WANT THEM TO CALL YOU?

(COURT AND CLERK CONFER)

THE COURT: WHY DON'T WE DO THIS: MAKE SURE BEFORE YOU LEAVE TODAY THAT MS. MORIYAMA HAS A NUMBER WHERE YOU CAN BE REACHED TOMORROW MORNING, AND DON'T CALL US, WE'LL CALL YOU. IF THERE'S A PROBLEM, SHE'LL CALL EACH AND EVERY ONE OF YOU. OTHERWISE, BE AT OPERA PLAZA, CONVENE THERE, AND WE'LL BRING YOU OVER AT 1:00. BUT BE THERE AT 12:30; OKAY?

SO HAVE YOUR LUNCH BEFOREHAND, PLEASE. WE'LL PROBABLY GET ONE BREAK IN BETWEEN, AND PLUNGE FORWARD.

AND THANK YOU VERY MUCH FOR BEING SO COOPERATIVE. AND I HOPE TOMORROW THAT YOUR ENTRANCE IN THE BUILDING IS UNEVENTFUL, AS FOR ALL OF YOURS.

OKAY. YOU MAY CONTINUE.

MR. FIGG: THANK YOU.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DR. WALLACE, HAVE YOU REVIEWED SOME OF THE ARGUMENTS THAT CETUS MADE TO THE PATENT & TRADEMARK OFFICE IN ORDER TO GET ITS PATENTS -- TO GET ITS '202 PATENT?

A. YES, I -- I HAVE REVIEWED SOME OF IT.

Q. IN PARTICULAR, SOME OF THE TECHNICAL ARGUMENTS THAT THEY MADE --

A. YES.

Q. -- THE SCIENTIFIC ARGUMENTS?

A. YES.

Q. DID YOU SEE ANYTHING IN THOSE ARGUMENTS TO SHOW WHAT THE CAPABILITIES A PERSON OF ORDINARY SKILL IN THE ART IN 1984 WERE?

A. YES, I DID.

Q. WHAT WAS THAT?

A. WELL, THERE WAS ONE DOCUMENT WHICH WAS A DECLARATION BY ONE OF THE SENIOR CETUS SCIENTISTS SUPPORTING A CLAIM WITHIN THE '202 PATENT.

Q. OKAY. I HAND YOU A COPY OF A DOCUMENT THAT WE'VE MARKED AS EXHIBIT A-99 AND ASK IF THAT IS THE DECLARATION THAT YOU'RE TALKING ABOUT.

A. YES. THIS IS A DECLARATION BY DR. HENRY ERLICH OF THE CETUS CORPORATION.

Q. DO YOU KNOW DR. ERLICH --

A. YES, I DO.

Q. -- OR KNOW OF HIM?

A. YES, I DO.

Q. WHO IS DR. ERLICH?

A. HE'S A -- AS I SAID, A SENIOR SCIENTIST, WELL-RESPECTED SCIENTIST, AT CETUS CORPORATION.

Q. WHAT DO YOU UNDERSTAND TO HAVE BEEN THE PURPOSE OF THIS

DECLARATION BY DR. ERLICH?

A. WELL, THIS WAS A DECLARATION SUBMITTED TO THE PATENT OFFICE DURING THE PROSECUTION OF THE '202 PATENT, AND THE PURPOSE WAS TO TRY TO OVERCOME A REJECTION OF ONE OF THE CLAIMS WITHIN THE '202 PATENT.

Q. AND THAT WAS CLAIM 14?

A. YEAH, THAT WAS CLAIM 14.

Q. I'VE PLACED A POSTER, A BLOWUP OF CLAIM 14 ON THE EASEL.

WHAT DO YOU UNDERSTAND CLAIM 14 TO COVER?

A. WELL, THE CLAIM READS:

"THE PROCESS OF CLAIM 1, WHEREIN SAID STEPS ARE CARRIED OUT SIMULTANEOUSLY ABOVE ROOM TEMPERATURE USING AN ENZYME THAT AFTER EXPOSED TO A TEMPERATURE OF ABOUT 65 DEGREES TO 90 DEGREES CENTIGRADE FORMS SAID EXTENSION PRODUCTS AT THE TEMPERATURE OF REACTION DURING STEPS (A) AND (C)."

SO IT'S A PROCESS WHICH IS . . . OR -- WHICH IS COVERED BY CLAIM 1 BUT WHICH USES AN ENZYME THAT DOES NOT BECOME INACTIVATED AT HIGHER TEMPERATURE AND ACTUALLY DOESN'T UNDERGO CYCLING OF DENATURATION AND RENATURATION.

I GUESS YOU COULD CALL IT A SIMULTANEOUS REACTION AS THE WORD SIMULTANEOUSLY IS IN THE CLAIM.

Q. HAVE YOU HEARD THIS REACTION REFERRED TO AS A SIMULTANEOUS REACTION BEFORE?

A. YEAH, I -- YES, I HAVE.

Q. OKAY. AND YOU INDICATED THAT THE ERLICH AFFIDAVIT WAS RESPONSIVE TO A REJECTION BY THE EXAMINER?

A. YES. AS -- AS I UNDERSTAND IT, THE EXAMINER SAID THAT THIS CLAIM WASN'T PATENTABLE BECAUSE THERE WERE NO EXPERIMENTS, NO EXAMPLES WITHIN THE PATENT WHICH SUPPORTED THE CLAIM. THE CLAIM REQUIRED A THERMOSTABLE ENZYME AND CONDITIONS FOR DOING THIS SIMULTANEOUS REACTION WHICH WEREN'T DESCRIBED IN THE APPLICATION ITSELF.

Q. HOW DID CETUS RESPOND TO THE EXAMINER'S REJECTION?

A. WELL, THE AFFIDAVIT BASICALLY SAYS THAT THE PROCESS OF CLAIM 14 WAS PATENTABLE BECAUSE A SCIENTIST OF ORDINARY SKILL COULD HAVE WORKED OUT THE CONDITIONS FOR DOING THESE PARTICULAR -- THIS PARTICULAR REACTION.

Q. AND WHAT EVIDENCE DID CETUS SUBMIT TO THE PATENT EXAMINER TO SUPPORT THAT ARGUMENT?

A. WELL, THEY SUBMITTED COPIES OF THE NOTEBOOKS OF MR. FALOONA, WHO WAS WORKING, I GUESS, UNDER THE DIRECTION OF DR. MULLIS, WHO IN TURN WAS WORKING UNDER THE DIRECTION OF DR. ERLICH, SHOWING EXPERIMENT -- HOW THE EXPERIMENTS HAD BEEN DONE AND HOW THE CONDITIONS HAD BEEN WORKED OUT TO PERFORM THE SIMULTANEOUS REACTION.

Q. AND THAT INCLUDED THE LABORATORY NOTEBOOK PAGES DESCRIBING THOSE EXPERIMENTS?

A. YES, THEY DID.

Q. THOSE ARE ATTACHED TO DR. ERLICH'S DECLARATION, I TAKE IT.

A. YES, THEY ARE.

Q. HAVE YOU REVIEWED THOSE LABORATORY NOTEBOOK PAGES?

A. YES, I'VE LOOKED AT THEM. I MUST ADMIT SOMETIME AGO, BUT I'VE LOOKED AT THEM, YES.

Q. CAN YOU SUMMARIZE THE CONDITIONS THAT CETUS -- THAT DR. MULLIS AND MR. FALOONA WERE ABLE TO USE TO MAKE THIS PROCESS OF CLAIM 14 WORK.

A. WELL, IT'S SUMMARIZED IN THE -- IN THE DECLARATION.

FIRST OF ALL, YOU NEEDED AN ENZYME THAT WOULDN'T BE INACTIVATED BY THE HEATING -- BY HEAT, BECAUSE THE REACTION NEEDED A HIGH TEMPERATURE TO -- TO -- TO WORK.

AND SO, FIRST OF ALL, YOU NEEDED AN ENZYME, A DNA POLYMERASE, BUT WHICH WAS CALLED A THERMOSTABLE DNA POLYMERASE, AND THEY ISOLATED THIS ENZYME FROM ANOTHER BACTERIA CALLED THERMUS AQUATICUS. AND USING THIS ENZYME, THEN, YOU COULD DO THE REACTION AT ELEVATED TEMPERATURES.

AND THEY VARIED TEMPERATURES, POSITIONS OF THE PRIMERS, AND REACTION CONDITIONS, THE COMPONENTS OF THE REACTION, TO -- TO GET THE REACTION TO WORK.

THE WAY THIS REACTION WORKS IS, IT'S THE SAME AS CLAIM 1. THAT'S WHAT THE CLAIM -- THIS CLAIM SAYS. THE PROCESS OF CLAIM 1, IN WHICH THE PRIMERS ANNEAL OR BIND TO THE SEPARATED TEMPLATE STRANDS, AND THEN PRIMER EXTENSION IS CARRIED OUT, BUT THIS TIME BY A THERMOSTABLE ENZYME, AN ENZYME THAT WILL WORK AT A HIGH TEMPERATURE.

AND THEN INSTEAD OF SUBJECTING IT TO A -- ANOTHER ROUND OF DENATURATION IN ORDER TO REMOVE THE PRIMER EXTENSION PRODUCT FROM THOSE NEWLY-CREATED DOUBLE-STRANDED TEMPLATES, THIS PROCESS OF STRAND REMOVAL OCCURS IN THE PRESENCE OF THE PRIMER AT THE TEMPERATURE OF THE REACTION.

SO IT -- IF THE PRIMER EXTENSION OCCURS, THE STRANDS ARE SEPARATED UNDER THE CONDITIONS OF THE EXPERIMENT, AND THE NEW PRIMER BINDS AND THE NEW STRAND IS MADE, AND SO ON AND SO ON. SO THE REACTION JUST CONTINUES AT A SINGLE TEMPERATURE.

AND THAT WAS THE BASIS OF -- THAT WAS THE ESSENCE OF THE EXPERIMENTS IN THE NOTEBOOK.

Q. IN THE EXPERIMENTS IN THE NOTEBOOKS, WERE ANY SPECIAL COMPONENTS ADDED TO THE REACTION?

A. YEAH. THERE WAS SEVERAL SET -- SEVERAL UNIQUE CONDITIONS THAT HAD TO BE USED IN ORDER TO GET THIS REACTION TO WORK. ONE WAS THE ENZYME, AS I SAID. THE OTHER WAS THE COMPONENTS OF THE REACTION.

THE REACTION INCLUDED A COMPONENT CALLED DIMETHYL SULFOXIDE, WHICH WAS -- WAS ADDED TO THE REACTION, AND BOVINE SERUM ALBUMIN, TWO COMPONENTS WHICH WERE CHOSEN TO TRY TO OPTIMIZE THIS REACTION.

Q. AND WHAT -- WHAT KINDS OF CONSTRAINTS WERE THERE ON THE PRIMERS IN THE EXPERIMENTS DESCRIBED IN THE NOTEBOOK PAGES?

A. WELL, IN THE NOTEBOOK PAGES, THE -- ONE CONSTRAINT THAT WAS DESCRIBED WAS THE DISTANCE BETWEEN THE PRIMERS; IN OTHER WORDS,

THE PROCESS AS WE'VE DESCRIBED IN CLAIM 1 ISN'T LIMITED TO SHORT PRIMER -- SHORT TEMPLATES OR LONG TEMPLATES AND IT'S NOT -- THE DISTANCE BETWEEN THE PRIMERS IS NOT CONSTRAINED.

BUT IN THIS PARTICULAR EXAMPLE, THEY FOUND THAT THE DISTANCE BETWEEN THE PRIMERS -- SHALL I PERHAPS SHOW THEM?

Q. SURE. YOU CAN USE THE POSTER, IF YOU'D LIKE.

A. THE DISTANCE BETWEEN THE END OF THE PRIMER ON ONE TEMPLATE STRAND AND THE END OF THE PRIMER ON THE OTHER TEMPLATE STRAND WAS RESTRICTED TO SIX TO EIGHT NUCLEOTIDES.

THEN THEY SHOWED THAT YOU COULD AMPLIFY TEMPLATES THEN THAT WERE OF DIFFERENT LENGTHS -- I THINK ONE WAS 58, ANOTHER ONE WAS 75 -- USING PRIMERS WHICH WERE CLOSE TOGETHER, BASICALLY.

(WITNESS RESUMES WITNESS STAND.)

Q. WERE THERE ANY CONSTRAINTS IN THE EXPERIMENTS DESCRIBED IN THE DECLARATION, ANY CONSTRAINTS WITH REGARD TO THE . . . LENGTH OF TIME THE REACTION WAS ALLOWED TO PROCEED?

A. THE TIME OF THE REACTION WAS -- THE REACTION WAS CARRIED OUT FOR VARIOUS LENGTHS OF TIME, BUT THE REACTION WORKED, FOR EXAMPLE -- FOR ONE PARTICULAR EXAMPLE, THEY HAD TO CARRY THE REACTION OUT FOR ONE DAY AND FOR SEVEN DAYS. SO THE REACTION TIME WAS CHANGED FROM HOURS TO DAYS, AND AS LONG AS SEVEN DAYS IN SOME CASES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) WITH RESPECT TO THE USE OF THIS COMPONENT YOU

CALLED BOVINE SERUM ALBUMIN -- I THINK IT'S ALSO CALLED BSA -- WHAT GUIDANCE DOES THE '202 PATENT SPECIFICATION GIVE THE READER WITH RESPECT TO BSA?

A. I DON'T RECALL BSA BEING MENTIONED.

Q. DOES THE '202 PATENT SAY THE PERSON SKILLED IN THE ART SHOULD USE BSA IN THE PROCESS DESCRIBED IN CLAIM 14?

A. NO. CLAIM 14 ISN'T RESTRICTED TO ANY OF THESE CONDITIONS THAT I DESCRIBED. IT DOESN'T SAY BSA; IT DOESN'T SAY DIMETHYL SULFOXIDE; IT DOESN'T SAY THE DISTANCE BETWEEN THE PRIMERS IS IMPORTANT.

Q. DOES THE SPECIFICATION OF THE '202 PATENT SAY ANYTHING ABOUT DIMETHYL SULFOXIDE?

A. NOT TO MY KNOWLEDGE.

Q. DOES . . . DOES THE '202 PATENT SPECIFICATION TEACH THAT THE PRIMER SHOULD BE WITHIN SIX TO EIGHT NUCLEOTIDES OF ONE ANOTHER FOR THIS REACTION OF CLAIM 14 TO WORK?

A. NO, IT DOES NOT. IT DOESN'T GIVE ANY GUIDANCE IN THAT REGARD.

Q. DOES THE '202 PATENT SPECIFICATION TEACH THAT ONE SHOULD USE LONG ANNEALING TIMES THAT YOU MENTIONED TO MAKE THE PROCESS OF CLAIM 14 WORK?

A. YOU MEAN LONG REACTION TIMES.

Q. I'M SORRY. LONG REACTION TIMES.

A. NO, IT DOES NOT.

Q. WELL, WHAT WAS CETUS' BASIS FOR ARGUING TO THE PATENT

EXAMINER THAT THIS PROCESS OF CLAIM 14 WAS ADEQUATELY DESCRIBED IN THE SPECIFICATION?

A. WELL, IN MY OPINION, THE POINT WAS THAT THE CONCEPTS OF PCR TAUGHT BY CLAIM 1, AND THAT ONCE YOU UNDERSTAND THAT, YOU SHOULD BE ABLE TO DO THE PROCESS OF CLAIM 14 THROUGH ORDINARY EXPERIMENTATION, OF TESTING CONDITIONS FOR THIS REACTION AND GETTING IT TO WORK.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DO YOU HAVE AN OPINION ABOUT WHETHER A -- AN ORDINARY SKILLED SCIENTIST WHO COULD FIGURE OUT ALL OF THE CONDITIONS THAT CETUS FIGURED OUT FOR MAKING CLAIM 14 WORK, WOULD THAT SAME ORDINARY SKILLED SCIENTIST -- LET ME STRIKE ALL OF THAT AND START OVER:

HOW WOULD YOU COMPARE THE AMOUNT OF EXPERIMENTATION REQUIRED OF AN ORDINARY SKILLED SCIENTIST TO WORK OUT THE CONDITIONS YOU'VE DESCRIBED FOR CLAIM 14 WITH THE AMOUNT OF EXPERIMENTATION THAT WOULD HAVE BEEN REQUIRED BY A SCIENTIST TO FOLLOW THE TEACHINGS OF DR. KHORANA'S PUBLICATIONS IN 1984 TO MAKE THE REACTIONS DESCRIBED THERE WORK?

A. WELL, THEY'RE DIFFERENT -- DIFFICULT TO COMPARE.

THE KHORANA PRIOR ART TEACHES THE PROCESS IN CLAIM 1 WE'VE BEEN TALKING ABOUT, AND THERE IS PLENTY OF PRECEDENT TO -- TO KNOW THAT THAT REACTION HAD A GOOD CHANCE OF WORKING. THERE WAS LOTS OF EXPERIENCE WITH PRIMER EXTENSION REACTIONS.

ON THE OTHER HAND, THE PROCESS OF CLAIM 14 REQUIRES

THIS SIMULTANEOUS EXTENSION, DENATURATION, PRIMER BINDING, EXTENSION, DENATURATION, ET CETERA, IN A -- IN ONE REACTION. THERE WAS LITTLE, IF ANY, PRIOR ART THAT WOULD HAVE SAID THAT THAT WOULD BE EXPECTED TO WORK.

SO IT'S DIFFICULT TO JUDGE. IT CERTAINLY TOOK AT LEAST AS MUCH SKILL TO . . . TO CARRY OUT THE PROCESS OF CLAIM 14 AS IT WOULD HAVE TO CARRY OUT THE PROCESS THAT KHORANA'S -- THAT THE KHORANA PRIOR ART DESCRIBES.

Q. OKAY.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DR. WALLACE, WE'VE BEEN SPENDING A LOT OF TIME TALKING ABOUT CLAIM 1, AND I WOULD NOW LIKE TO TURN TO SOME OF THE OTHER CLAIMS OF THE '202 PATENT; IN PARTICULAR, STARTING WITH CLAIM 2.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) I'VE PLACED A BLOWUP OF CLAIM 2 ON THE EASEL.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) AND CAN YOU EXPLAIN WHAT CLAIM 2 COVERS.

A. YES. FOR SIMPLICITY HERE, WE CAN SAY THAT CLAIM 1 COVERS (A), (B) AND (C). AND (A) IS THE FIRST ROUND OF -- OF PRIMER EXTENSION; (B) IS THE DENATURATION STEP, AND (C) IS THE SECOND ROUND OF PRIMER EXTENSION, WITH A TOTAL OF TWO ROUNDS OF AMPLIFICATION.

AND CLAIM 2, THEN, JUST SAYS THAT:

"THE PROCESS OF CLAIM 1 WHERE STEPS (B) AND

(C) ARE REPEATED AT LEAST ONCE."

SO (B) IS THE DENATURATION OF THE PRIMER EXTENSION PRODUCT, AND (C) IS THE NEXT ROUND OF PRIMER EXTENSION.

AND SO CLAIM 2, IF YOU COUPLED CLAIM 1 PLUS CLAIM 2, YOU WOULD HAVE HAD A TOTAL OF -- A MINIMUM OF THREE ROUNDS OF AMPLIFICATION.

Q. DO YOU HAVE AN OPINION AS TO WHETHER EACH OF DR. KHORANA'S ARTICLES, PUBLICATIONS WE'VE BEEN TALKING ABOUT WOULD HAVE DISCLOSED TO A PERSON OF ORDINARY SKILL IN THE ART THE REACTION DESCRIBED IN CLAIM 2?

A. OH, YES. THE KHORANA PRIOR ART DID NOT RESTRICT ITSELF TO JUST TWO OR THREE, FOR THAT MATTER, ROUNDS OF CYC -- OF AMPLIFICATION.

Q. IN FACT, THE PANET PAPER, I THINK, REFERRED TO MULTIPLE ROUNDS, IS THAT CORRECT, MULTIPLE CYCLES?

A. I BELIEVE THAT'S CORRECT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DO YOU HAVE AN UNDERSTANDING AS TO WHETHER ANY CLAIM IN THE '202 PATENT REQUIRES MORE THAN THREE ROUNDS OF -- THREE CYCLES OF HEATING, COOLING, PRIMER EXTENSION?

A. TO MY KNOWLEDGE, NO, ALTHOUGH I THINK ONE OF THE LATER CLAIMS MIGHT . . . IT'S POSSIBLE THAT ONE OF THE -- ONE OF THE PRIOR CLAIMS MIGHT GO TO FOUR ROUNDS BECAUSE OF, I THINK, CLAIM 11, WHICH WE'LL BE GETTING TO.

Q. OKAY. LET'S FOCUS ON THE NEXT CLAIM IN THE PATENT, CLAIM 3.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) AND I'VE PLACED A BLOWUP OF CLAIM 3 ON THE -- THE EASEL.

THAT CLAIM READS: "THE PROCESS OF CLAIM 1, WHEREIN SAID STEP (B) IS ACCOMPLISHED BY DENATURING."

DO YOU HAVE AN OPINION AS TO WHETHER THE PROCESS COVERED BY THIS CLAIM WAS DESCRIBED IN THE KHORANA PRIOR ART?

A. YES, IT WAS DESCRIBED. YOU MUST REMEMBER THAT CLAIM 1 IS EXTREMELY BROAD. IT COVERS -- (B) SAYS "SEPARATING THE PRIMER EXTENSION PRODUCTS." AND THAT COULD BE SEPARATIONS THAT OCCUR BY ANY NUMBER OF MEANS. THE NORMAL MEANS WOULD BE BY DENATURATION, WHICH CLAIM 3 COVERS. BUT I GUESS THE CLAIM COVERS OTHER METHODS.

AND CLAIM 3 SIMPLY SAYS -- IS ACCOMPLISHED BY DENATURATION. AND THAT WAS EXACTLY WHAT THE KHORANA PRIOR ART WAS TEACHING.

Q. OKAY. I'LL NOW PUT CLAIM 4 ON THE EASEL.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) CLAIM 4 READS: "THE PROCESS OF CLAIM 3, WHEREIN STEP (B) IS CAUSED BY HEATING."

DO YOU HAVE AN OPINION AS TO WHETHER THE SUBJECT MATTER CLAIMED IN CLAIM 4 WAS DESCRIBED IN DR. KHORANA'S PUBLICATIONS?

A. YES, THIS SUBJECT MATTER WAS COVERED IN THE KHORANA PRIOR ART.

THIS IS JUST A SPECIFIC EXAMPLE OF A WAY OF DOING

DENATURATION, BY HEATING. THERE ARE OTHER WAYS OF DENATURING, BUT KHORANA WAS SPECIFICALLY TALKING ABOUT DENATURATION BY HEATING, SO THIS IS JUST A -- THE PROCESS OF THE PREVIOUS CLAIM WE TALKED ABOUT, WHERE THE DENATURATION IS ACCOMPLISHED BY HEATING.

Q. AND, AGAIN, DENATURATION IS THE SEPARATION OF THE STRANDS SO THAT THE PRIMERS CAN ANNEAL TO THEM.

A. EXACTLY.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) THE NEXT CLAIM I'D LIKE TO TALK ABOUT IS CLAIM 6.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) CLAIM 6 READS: "THE PROCESS OF CLAIM 1, WHEREIN STEPS (A) AND (C) ARE ACCOMPLISHED USING AN ENZYME."

AND I'VE PLACED A POSTER OF THIS CLAIM ON THE EASEL.

DO YOU HAVE AN OPINION AS TO WHETHER THE SUBJECT MATTER OF THIS CLAIM WAS TAUGHT IN DR. KHORANA'S PRIOR ART?

A. YES. THIS IS EXACTLY WHAT DR. KHORANA'S PRIOR ART TEACHES, AND IN THIS CASE THE ENZYME THAT HE WAS USING WAS DNA POLYMERASE.

AGAIN, YOU MUST REALIZE THAT THE PROCESS OF CLAIM 1 IS VERY BROAD, SO STEPS (A) AND (C) ARE PRIMER EXTENSION STEPS, BUT THEY'RE SO BROAD, THEY DON'T SPECIFY IN THIS CLAIM THAT AN ENZYME IS USED. AND THIS CLAIM SIMPLY SPECIFIES THAT AN ENZYME

CAN BE USED. IT DOESN'T SPECIFY A DNA POLYMERASE, JUST AN ENZYME.

Q. WAS -- WHEN THIS PATENT APPLICATION WAS FILED IN EARLY 1985, WAS THERE ANY WAY OF CARRYING OUT A PRIMER EXTENSION REACTION WITH SOMETHING OTHER THAN AN ENZYME?

A. NOT TO MY KNOWLEDGE.

Q. IS SUCH A PROCESS KNOWN TODAY?

A. NOT TO MY KNOWLEDGE.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) AND, SPECIFICALLY, WHAT WAS THE ENZYME DESCRIBED IN DR. KHORANA'S PUBLICATIONS?

A. WELL, ACTUALLY, DR. KHORANA DISCUSSED SEVERAL KINDS OF DNA POLYMERASE: DNA POLYMERASE FROM E. COLI, AS DR. KORNBERG TALKED ABOUT, AND OTHER DNA POLYMERASES THAT THEY WERE USING IN THE LAB. THE ENZYME WAS DNA POLYMERASE.

Q. OKAY.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) I'VE PLACED A POSTER OF CLAIM 7 ON THE EASEL.

THIS CLAIM LISTS A NUMBER OF ENZYMES, AND THIS ONE IS DEPENDENT ON CLAIM 6 RATHER THAN CLAIM 1, OR IT REFERS BACK TO CLAIM 6.

IS IT YOUR RECOLLECTION CLAIM 6 REFERS TO CLAIM 1?

A. YES.

Q. OKAY. THIS CLAIM READS: "THE PROCESS OF CLAIM 6, WHEREIN SAID ENZYME IS SELECTED FROM THE GROUP

CONSISTING OF E. COLI DNA POLYMERASE 1, KLENOW FRAGMENT OF E. COLI DNA POLYMERASE 1, T4 DNA POLYMERASE, REVERSE TRANSCRIPTASE, WHEREIN THE TEMPLATE IS RNA" -- I THINK THERE'S A TYPO -- "OR DNA AND THE EXTENSION PRODUCT IS DNA, AND AN ENZYME THAT AFTER BEING EXPOSED TO A TEMPERATURE OF ABOUT 65 TO 90 DEGREES CENTIGRADE FORMS SAID EXTENSION PRODUCTS AT THE TEMPERATURE OF REACTION DURING STEPS (A) AND (C)."

DO YOU HAVE AN OPINION AS TO WHETHER THE -- WHETHER SUBJECT MATTER THAT IS COVERED BY THIS CLAIM WAS DESCRIBED IN DR. KHORANA'S PRIOR ART?

A. YES, I DO. DR. KHORANA EXPLICITLY MENTIONED E. COLI DNA POLYMERASE 1 AS THE ENZYME THEY WERE MOST OFTEN USING. HE ALSO USED -- WHICH IS -- WHICH IS THE FIRST ENZYME IN THE LIST. HE ALSO USED T4 DNA POLYMERASE, I BELIEVE.

THE OTHER ENZYMES, THE KLENOW FRAGMENT OF E. COLI DNA POLYMERASE 1, WASN'T AVAILABLE OR READILY AVAILABLE IN THE EARLY '70'S, AND SO THAT WOULDN'T HAVE BEEN USED BY KHORANA, AND REVERSE TRANSCRIPTASE ALSO WASN'T DISCOVERED UNTIL LATER.

AND ALSO, IT'S DISCLOSING A THIRD, HEAT-STABLE ENZYME. AGAIN, THAT HAD BEEN PREVIOUSLY DESCRIBED BY OTHERS, BUT NOT BY DR. KHORANA'S LAB.

Q. THE CLAIM MENTIONS THE LANGUAGE, "THE ENZYME" -- OR "SAID ENZYME IS SELECTED FROM THE GROUP CONSISTING OF" ALL OF THESE THINGS.

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SO IS IT YOUR UNDERSTANDING THAT IF ANY ONE OF THESE IS USED, IT'S COVERED BY THE CLAIM?

A. THE WAY I WOULD UNDERSTAND IT IS THAT IF ANY ONE WAS USED, IT'S COVERED, YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) NOW, CLAIM 8, WHICH I'VE PLACED IN THE EASEL, READS:

"THE PROCESS OF CLAIM 7, WHEREIN SAID NUCLEIC ACID IS DOUBLE STRANDED AND THE STRANDS ARE SEPARATED BY DENATURING BEFORE OR DURING STEP (A)."

DO YOU HAVE AN OPINION AS TO WHETHER THE PROCESS COVERED BY THIS CLAIM WAS DESCRIBED IN DR. KHORANA'S PRIOR ART?

A. YES. THIS CLAIM JUST REITERATES AGAIN THAT DOUBLE-STRANDED DNA CAN BE DENATURED AND SUBJECTED TO PRIMER EXTENSION.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) AND THIS CLAIM SPECIFIES THAT THE NUCLEIC ACID REFERRED TO IN THE CLAIM IS DOUBLE-STRANDED.

A. RIGHT.

Q. WAS THAT DISCLOSED IN DR. KHORANA'S PRIOR ART?

A. A DOUBLE-STRANDED NUCLEIC ACID COULD BE A DNA OR AN RNA. DR. KHORANA'S LAB WAS DEALING WITH DOUBLE-STRANDED DNA EXPLICITLY.

Q. THAT'S WHAT THEY REFERRED TO AS DUPLEXES, DNA DUPLEXES?

A. I THINK IT WAS DUPLEX DNA OR DUPLEX TRNA GENE.

Q. UH-HUH.

6

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) THIS CLAIM WILL TEST MY ABILITY TO PRONOUNCE ONE OF THESE BIG WORDS.

CLAIM 9, WHICH I'VE PLACED ON THE EASEL SAYS:

"THE PROCESS OF CLAIM 1, WHEREIN SAID NUCLEIC ACID IS DNA AND SAID PRIMERS ARE OLIGODEOXYRIBONUCLEOTIDES."

CAN YOU EXPLAIN, FIRST OF ALL, WHAT THAT MEANS; AND, SECONDLY, WHETHER YOU HAVE AN OPINION AS TO WHETHER OR NOT THIS PROCESS WAS DESCRIBED BY DR. KHORANA'S PRIOR ART.

A. OKAY. IF YOU REMEMBER BACK TO THE DESCRIPTION OF CLAIM 1, IT STARTS WITH A NUCLEIC ACID, AT LEAST ONE SPECIFIC NUCLEIC ACID SEQUENCE.

NOW, NUCLEIC ACID SEQUENCE CAN BE A DNA OR IT CAN BE AN RNA. AND IT USES, LATER ON IN THE CLAIM, OLIGONUCLEOTIDE PRIMERS. AGAIN, THOSE PRIMERS CAN BE A DNA OR AN RNA.

AND THIS CLAIM SIMPLY STATES THAT THE NUCLEIC ACID IS DNA AND THAT THE PRIMERS ARE OLIGODEOXYRIBONUCLEOTIDES, WHICH MEANS OLIGONUCLEOTIDES MADE OUT OF DNA BUILDING BLOCKS.

AND THIS IS PRECISELY THE PROCESS CLAIMED -- DESCRIBED BY THE KHORANA PRIOR ART.

Q. SO THIS -- THIS BIG LONG WORD HERE JUST MEANS SHORT PIECES OF DNA USED AS PRIMERS.

A. YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) HERE'S A CLAIM YOU REFERRED TO EARLIER. I'VE PLACED CLAIM 11 ON THE EASEL, AND IT READS:

"THE PROCESS OF CLAIM 1, WHEREIN SAID MIXTURE OF NUCLEIC ACIDS USED IN STEP (A) IS THE PRODUCT OF STEP (C)."

DO YOU HAVE AN OPINION AS TO WHETHER OR NOT THE PROCESS OF THIS CLAIM WAS DESCRIBED IN DR. KHORANA'S PRIOR ART?

A. WELL, THE WAY I UNDERSTAND THIS CLAIM, THE PRODUCT OF STEP (C) OF CLAIM 1, WHICH IS A TEMPLATE THAT HAS UNDERGONE TWO ROUNDS OF PRIMER EXTENSION, CAN BE USED AS THE STARTING TEMPLATE AT STEP (A), AND THEN TAKEN THROUGH IT AGAIN.

SO IT SIMPLY MEANS YOU ARE REPEATING (A) THROUGH (C) WITH THE ORIGINAL PRODUCT OF STEP (C).

SO THE WAY I UNDERSTAND IT, IT WOULD MEAN THAT YOU HAVE TAKEN A PARTICULAR NUCLEIC ACID SEQUENCE THROUGH FOUR ROUNDS OF PRIMER EXTENSION.

Q. AND WOULD THIS INVOLVE PRIMER ADDITION AT DIFFERENT STAGES?

A. IT DOESN'T SAY THAT YOU . . . YES, I'M SORRY. EXCUSE ME.

TO THAT TEMPLATE, YOU WOULD ADD FRESH PRIMER. YOU WOULD -- BECAUSE YOU'RE INTRODUCING IT AT STEP (A), WHICH SAYS "TREATING THE STRANDS WITH TWO OLIGONUCLEOTIDE PRIMERS."

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) AND I HAVE THE BLOWUP OF PAGE 5220 OF THE PANET ARTICLE.

DOES THAT ARTICLE IN PARTICULAR SAY ANYTHING ABOUT

ADDING ADDITIONAL PRIMERS IN STEPS SUBSEQUENT TO THE FIRST STEP?

A. YEAH, I BELIEVE . . . CAN I --

Q. WOULD YOU LIKE TO COME DOWN?

THE COURT: YOU MAY STEP DOWN, SURE.

(PAUSE IN PROCEEDINGS)

THE WITNESS: THE LANGUAGE IS: "TO FORM THE APPROPRIATE TEMPLATE-PRIMER COMPLEX, IT WAS NECESSARY TO HEAT AND COOL IN THE PRESENCE AN OF EXCESS . . . OF THE APPROPRIATE PRIMERS."

"AND (C) IN ORDER TO PERFORM MULTIPLE CYCLES OF REPAIR REPLICATION, IT WAS NECESSARY TO ADD, AFTER EACH CYCLE, FRESH AMOUNTS OF THE PRIMERS SO AS TO MAINTAIN THE APPROPRIATE PRIMER RATIOS."

SO I WOULD SAY, YES, IT'S A -- IT'S CLEARLY INDICATING THAT YOU NEED TO ADD FURTHER PRIMERS TO A PRODUCT IN THE AMPLIFICATION REACTION.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DR. WALLACE, I'VE PUT CLAIM 12 ON THE EASEL NOW.

THIS CLAIM READS: "THE PROCESS OF CLAIM 11, WHEREIN THE PRIMERS EMPLOYED ARE DIFFERENT FROM THE PRIMERS EMPLOYED IN THE PROCESS FOR PRODUCING THE PRODUCT OF STEP (C) USED IN STEP (A)."

DO YOU HAVE AN OPINION AS TO WHETHER OR NOT THE PROCESS COVERED BY THIS CLAIM WAS DESCRIBED IN THE KHORANA PRIOR ART?

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A. YES, I DO. THESE . . . IT'S ALWAYS DIFFICULT TO SEE -- YOU HAVE TO REMEMBER BACK TO CLAIM 11, WHERE IT SAID THAT THE PRODUCT OF STEP (C) BECAME THE TEMPLATE INTRODUCED AT STEP (A).

BUT REMEMBER THAT YOU CAN ADD -- STEP (A) INCLUDES ADDING FRESH PRIMERS, OR ADDING PRIMERS. AND THIS CLAIM SIMPLY SAYS THAT THOSE PRIMERS ARE DIFFERENT THAN THE ONES USED TO ORIGINALLY PRODUCE THE PRODUCT OF STEP (C), WHICH IS TWO ROUNDS OF AMPLIFICATION.

Q. DO YOU HAVE AN OPINION AS TO WHETHER OR NOT A PERSON SKILLED IN THE ART IN 1984 WOULD HAVE UNDERSTOOD THE SCOPE OF THIS CLAIM OR WHAT THIS CLAIM IS COVERING?

A. WELL, IT'S NOT TOTALLY CLEAR WHY YOU WOULD WANT TO ADD DIFFERENT . . . DIFFERENT PRIMERS AT THIS STEP, AND IT'S ALSO NOT CLEAR EXACTLY HOW MANY PRIMERS ARE IN THE REACTION THAT YOU'RE TALKING ABOUT.

THE PRODUCT OF STEP (C) OF CLAIM 1 PRESUMABLY HAS PRIMERS LEFT, AND YOU'RE ADDING TO THE PRODUCT OF STEP (C) MORE PRIMERS IN -- YOU'RE INTRODUCING IT IN STEP (A). SO IT'S NOT CLEAR TO ME HOW MANY PRIMERS ARE IN THIS REACTION, BUT . . . THAT'S WHAT IT SAYS.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) I'VE NOW PLACED CLAIM 13 ON THE EASEL.

THIS ONE READS: "THE PROCESS OF CLAIM 12, WHEREIN THE PRIMERS EMPLOYED RESULT IN THE AMPLIFICATION OF A SMALLER SEQUENCE CONTAINED WITHIN THE SEQUENCE BEING

AMPLIFIED IN THE PROCESS FOR PRODUCING THE PRODUCT OF STEP (C) USED IN STEP (A)."

DO YOU HAVE AN OPINION AS TO WHETHER THE PROCESS COVERED BY THIS CLAIM WAS DESCRIBED IN DR. KHORANA'S PRIOR ART?

A. WELL, FIRST OF ALL, YOU NEED TO UNDERSTAND WHAT THIS CLAIM IS, AND REMEMBER IT'S THE PROCESS OF CLAIM 12 WHICH IN TURN WAS THE PROCESS OF CLAIM 11, WHICH I BELIEVE WAS IN TURN REFERRING BACK TO CLAIM 1.

AND THE POINT IS, IS THAT THE PRODUCT OF STEP (C) IS USED AS THE TEMPLATE AND REINTRODUCED AT STEP (A), AND NEW PRIMERS ARE ADDED, AND THOSE NEW PRIMERS HAVE THE -- ARE SPECIFICALLY DESIGNED TO PRODUCE A SMALLER AMPLIFICATION SEQUENCE CONTAINED WITHIN THE SEQUENCE BEING AMPLIFIED.

AND THIS WOULD . . . I THINK IT'S BECOME KNOWN AS USING NESTED PRIMERS. YOU HAVE OUTSIDE PRIMERS AND THEN INSIDE PRIMERS.

THAT'S THE WAY I UNDERSTAND THIS TO READ.

BUT IF YOU REALLY THINK ABOUT IT, IT'S SIMPLY SAYING THAT AN AMPLIFICATION PRODUCT CAN SERVE AS THE TEMPLATE FOR AN AMPLIFICATION.

SINCE YOU'VE ALREADY HEARD THAT THE PRODUCT OF AN AMPLIFICATION REACTION IS REALLY NO DIFFERENT THAN THE STARTING DNA, IT WOULD NOT BE SURPRISING THAT SUCH A -- SUCH A PROCESS WOULD WORK. IT'S JUST A DIFFERENT KIND OF TEMPLATE.

Q. DO YOU THINK A PERSON SKILLED IN THE ART IN 1984 WOULD HAVE

UNDERSTOOD THE SCOPE OF THIS CLAIM OR WHAT THIS CLAIM WAS ACTUALLY COVERING BASED ON THE TEACHINGS OF THE '202 PATENT?

A. WELL, AS I SAY, IT'S A LITTLE CONFUSING BECAUSE IT DOESN'T REALLY SAY JUST HOW MANY PRIMERS ARE GOING TO BE PRESENT IN STEP (A) AFTER FOLLOWING THE TEACHINGS OF THIS CLAIM. SO IT WOULD BE CONFUSING FROM THAT POINT OF VIEW.

(PAUSE IN PROCEEDINGS)

THE WITNESS: IT DOES NOT SAY, FOR EXAMPLE, THAT YOU SHOULD REMOVE THE PRIMERS FROM THE TEMPLATE, THE PRODUCT OF STEP (C), BEFORE INTRODUCING IT INTO THE REACTION OF DIFFERENT PRIMERS. THAT PROBABLY WOULD HAVE MADE MORE SENSE, BUT . . .

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) REFERRING NOW TO CLAIM 15, IT READS:

"THE PROCESS OF CLAIM 1, WHEREIN THE TWO PRIMERS IN STEPS (A) AND (C) ARE EACH PRESENT IN A MOLAR RATIO OF AT LEAST 1,000 TO ONE, PRIMER TO COMPLEMENTARY STRAND."

DO YOU HAVE AN OPINION AS TO WHETHER THE SUBJECT MATTER OF THIS CLAIM WAS DESCRIBED BY THE KHORANA PRIOR ART TO A PERSON OF ORDINARY SKILL IN 1984?

A. WELL, FIRST, I SHOULD EXPLAIN WHAT "MOLAR" MEANS.

"MOLAR" IS THE SCIENTIFIC WAY OF DESCRIBING CONCENTRATIONS OF THINGS, AND IT RELATES REALLY TO THE NUMBER OF MOLECULES, AND A MOLAR RATIO IS A RATIO OF MOLECULES IN THE REACTION.

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SO THIS IS SIMPLY SAYING THAT THE RATIO OF PRIMER MOLECULES TO COMPLEMENTARY STRAND MOLECULES SHOULD BE AT 1,000 TO ONE.

NOW, THE KHORANA PRIOR ART CLEARLY SAYS YOU NEED AN EXCESS. AND YOU WOULD ASK YOURSELF, WELL, WHY WOULD YOU WANT A THOUSAND TO ONE?

BUT I THINK WHAT YOU NEED TO UNDERSTAND IS THAT -- WE'VE ALREADY GONE THROUGH THIS -- THAT WHEN ONE TEMPLATE GOES TO TWO, TWO TEMPLATES GO TO FOUR, FOUR TEMPLATES GO TO EIGHT, THIS IS A -- AN EXPONENTIAL GROWTH,

IN ORDER TO GO THROUGH THAT 10 TIMES, AFTER YOU'VE GONE THROUGH IT 10 TIMES, ONE MOLECULE OF TEMPLATE WOULD HAVE ACCUMULATED TO THE LEVEL OF ABOUT 1,000 MOLECULES, DEPENDING ON THE EXACT EFFICIENCY. AND EVERY TIME YOU'RE GOING THROUGH THAT REACTION, YOU'RE CONSUMING PRIMER.

SO IT WOULD BE CLEAR THAT IN ORDER TO DO A REACTION FOR ANY EXTENSIVE NUMBER OF CYCLES, YOU WOULD HAVE NEEDED A LARGE EXCESS OF PRIMER; FOR EXAMPLE, A THOUSAND TO ONE.

A THOUSAND TO ONE WOULD NOT HAVE SUPPORTED 20 ROUNDS OF AMPLIFICATION, FOR EXAMPLE.

Q. REFERRING TO THE NSF GRANT APPLICATION, PAGE 18 OF WHICH I'VE PLACED ON THE EASEL, CAN YOU EXPLAIN HOW THAT DOCUMENT SUGGESTS OR TEACHES THAT AN EXCESS ON THE ORDER OF A THOUSAND TO ONE WOULD BE OBVIOUS.

A. WELL, IT DOESN'T SAY EXACTLY. IT SAYS AN EXCESS OF THE TWO

APPROPRIATE PRIMERS.

AND THE -- AT EVERY CYCLE, ONE PRIMER IS USED UP. THIS PRIMER BINDS HERE (INDICATING), THIS PRIMER BINDS HERE (INDICATING), AND YOU CONSUME IT BY MAKING A COPY OF THE TEMPLATE STRAND.

SO THAT PRIMER IS NO LONGER AVAILABLE.

IN ORDER TO DO THAT AGAIN, YOU NEED ADDITIONAL PRIMERS, AND THEREFORE IN ORDER TO DO IT MANY TIMES, YOU'RE GOING TO NEED A VERY LARGE EXCESS.

(WITNESS RESUMES WITNESS STAND.)

Q. WHAT WAS THE RELATIVE DIFFICULTY OF USING A THOUSAND TO ONE EXCESS IN 1972 WHEN DR. KHORANA'S LAB WAS DOING ITS WORK COMPARED WITH 1984, THE DATE OF THE CETUS PATENT?

A. WELL, THE -- THE PRIMERS THAT THEY WERE USING WERE RATHER . . . PRECIOUS, I GUESS IS THE WORD. IN FACT, I THINK DR. KHORANA USED THE WORD "HARD WON." THEY WERE VERY DIFFICULT TO MAKE, AND ONCE YOU HAD THEM, YOU WANTED TO BE VERY JUDICIOUS ABOUT HOW YOU USED THEM.

AND TO -- TO SQUANDER PRIMER BY USING HUGE EXCESSES WOULD HAVE BEEN . . . VERY . . . FOOLHARDY AND PROBABLY -- PROBABLY IMPOSSIBLE IN TERMS OF TRYING TO GET THE -- THOSE EXCESSES, A THOUSAND TO ONE, FOR EXAMPLE.

Q. BUT, AS WE'VE DISCUSSED, IN 1984, THEY WERE MORE READILY AVAILABLE?

A. WELL, CERTAINLY YOU COULD PUSH A BUTTON AND -- AND GET ANY

SEQUENCE YOU WANTED, AND . . . SO THEY WERE MORE READILY AVAILABLE TO THE SCIENTIFIC COMMUNITY AT LARGE.

Q. AND WERE EXCESSES ON THE ORDER OF A THOUSAND TO ONE READILY ACCESSIBLE TO A PERSON OF ORDINARY SKILL IN 1984?

A. WELL, THEY -- THEY WERE, BUT YOU ALSO MUST CONSIDER THE FACT THAT WE'RE TALKING ABOUT MOLAR RATIOS. I SAID THAT MOLAR RATIO MEANS THE NUMBER OF MOLECULES.

BY 1984, WE WERE USED TO USING SMALLER AMOUNTS OF TEMPLATE THAN DR. KHORANA'S LAB WAS USING. THAT HAD A LOT -- A LOT TO DO WITH ANALYTICAL TECHNIQUES. THEY WERE JUST BETTER, MORE SENSITIVE IN 1984.

AND SO WHEN YOU'RE THINKING ABOUT EXCESSES, YOU CAN ACHIEVE EXCESSES IN ONE OF TWO WAYS; MOLAR EXCESSES, THAT IS. ONE IS TO INCREASE THE AMOUNT OF PRIMER, AND THE OTHER IS TO DECREASE THE AMOUNT OF TEMPLATE.

AND SO, YEAH, I THINK THAT YOU WOULD BE EASILY -- EASILY HAVE BEEN ABLE TO ACHIEVE THOSE RATIOS.

Q. WELL, WHY WERE YOU ABLE TO WORK WITH MUCH LOWER AMOUNTS OF TEMPLATE OR DNA IN 1984 THAN DR. KHORANA WAS ABLE TO WORK WITH IN 1972?

A. WELL, IT HAD A LOT TO DO WITH, AS I SAY, ANALYTICAL TECHNIQUES.

DR. KHORANA'S LAB WAS USING -- DIDN'T HAVE ACCESS TO TECHNIQUES THAT WE HAD IN 1984, SUCH AS GELELECTROPHORESIS, AND HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY, AND ALL KINDS OF OTHER

TECHNOLOGIES THAT CAME TO BEING IN THE INTERIM TIME PERIOD, THE EARLY '70'S TO THE EARLY '80'S. AND THOSE TECHNIQUES JUST CAME -- WHAT CAME WITH THEM WAS MORE SENSITIVITY.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) CLAIM 17, WHICH I'VE PLACED ON THE EASEL, SAYS:

"THE PROCESS OF CLAIM 1, WHEREIN AT LEAST ONE PRIMER CONTAINS AT LEAST ONE NUCLEOTIDE WHICH IS NOT COMPLEMENTARY TO THE SPECIFIC SEQUENCE TO BE AMPLIFIED."

DO YOU HAVE AN OPINION AS TO WHETHER THE SUBJECT MATTER OF THIS CLAIM WAS DESCRIBED IN THE PRIOR ART AND DR. KHORANA'S PRIOR ART?

A. WELL, THE SUBJECT MATTER OF THIS CLAIM WAS NOT REALLY EXPLICITLY TAUGHT BY THE KHORANA PRIOR ART. DR. KHORANA WASN'T USING PRIMERS WHICH DID NOT PERFECTLY MATCH THE TEMPLATES. THAT WASN'T REALLY WHAT HE WAS AFTER.

BUT IN THE GENERAL FIELD OF MOLECULAR BIOLOGY, BIOTECHNOLOGY, THERE WAS A PROCESS WHICH USED PRIMERS WHICH CONTAINED AT LEAST ONE NUCLEOTIDE, WHICH IS NOT COMPLEMENTARY, AND THAT PROCESS I SORT OF ALREADY ALLUDED TO EARLIER IN ONE OF MY OWN PUBLICATIONS, WAS CALLED IN VITRO MUTAGENESIS, WHICH IS A LONG WORD, WHICH BASICALLY MEANS THAT YOU CAN CHANGE THE SEQUENCE OF THE -- OF A PARTICULAR SEQUENCE IN A GENE BY USING AN OLIGONUCLEOTIDE PRIMER WHICH CONTAINS A DIFFERENT SEQUENCE.

AND SO, THEREFORE, IT WAS KNOWN THAT THESE PRIMERS WOULD PRIME -- THESE KINDS OF PRIMERS, WHICH HAD AT LEAST ONE NUCLEOTIDE WHICH IS NOT COMPLEMENTARY, WOULD NEVERTHELESS PRIME IN A DNA POLYMERASE REACTION. THAT WAS THE BASIS OF THE PROCESS CALLED IN VITRO MUTAGENESIS.

Q. AND I BELIEVE YOU TESTIFIED EARLIER THAT THAT -- THAT PROCEDURE IS DESCRIBED IN YOUR ARTICLE IN SCIENCE MAGAZINE THAT WE MARKED AS EXHIBIT A-108?

A. (WITNESS SEARCHES THROUGH DOCUMENTS.) YES.

Q. DO YOU HAVE AN OPINION AS TO WHETHER OR NOT THE SUBJECT MATTER OF CLAIM 17 WOULD HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN 1984 IN VIEW OF THE TEACHINGS OF THE KHORANA PRIOR ART AND YOUR PAPER, EXHIBIT A-108?

A. OH, YES, I THINK IT WOULD HAVE BEEN OBVIOUS, NOT JUST BASED ON MY PAPER, BUT THERE WERE SEVERAL LABORATORIES DOING PRIMER EXTENSION REACTIONS WITH PRIMERS WHICH CONTAINED AT LEAST ONE NUCLEOTIDE WHICH WAS NOT COMPLEMENTARY, AND THAT WOULD HAVE BEEN WELL-KNOWN TO ONE IN 1984. SO, YES, IT WOULD HAVE BEEN OBVIOUS.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) NOW, DR. WALLACE, ALL OF THESE CLAIMS WE'VE BEEN TALKING ABOUT WERE DEPENDENT OR REFERRED BACK TO CLAIM 1. BUT CLAIM 19, WHICH I'VE PLACED ON THE BOARD, DOES NOT REFER BACK TO ANY EARLIER CLAIM.

AND I'D LIKE FOR YOU TO, FIRST OF ALL, EXPLAIN WHAT CLAIM 19 COVERS, AND THEN I'LL ASK YOU SOME QUESTIONS ABOUT ITS

RELATIONSHIP TO THE KHORANA PRIOR ART.

SO PERHAPS YOU CAN DO THAT WITH OUR LITTLE MODEL HERE AGAIN, WHICH WE HAVEN'T WORN OUT YET.

(PAUSE IN PROCEEDINGS)

THE WITNESS: WELL, FIRST OF ALL, WE COULD GO THROUGH THE CLAIM, BUT IN -- GENERALLY, IT'S ESSENTIALLY THE SAME PROCESS WE'RE TALKING ABOUT WITH CERTAIN RESTRICTIONS OR CERTAIN SPECIFICS ADDED, AND NOW YOU SEE THAT IT INVOLVES FOUR STEPS RATHER THAN THE THREE STEPS EARLIER.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) OKAY. PLEASE PROCEED.

A. SO IT IS A PROCESS FOR AMPLIFYING A SPECIFIC NUCLEIC ACID SEQUENCE CONTAINED IN A DOUBLE-STRANDED DNA WHICH PROCESS COMPRISES.

SO NOW IT'S LIMITED TO A DOUBLE-STRANDED DNA. THIS IS OUR DOUBLE-STRANDED DNA (INDICATING).

AND IN STEP (A), YOU SEPARATE THE STRANDS OF DNA BY PHYSICAL, CHEMICAL OR ENZYMATIC MEANS.

HEATING IS A PHYSICAL MEANS. YOU CAN THEN SEPARATE THE TWO STRANDS BY HEATING THEM, FOR EXAMPLE.

STEP (B), "TREATING THE SINGLE STRANDS WITH TWO OLIGODEOXYRIBONUCLEOTIDE PRIMERS" -- REMEMBER THOSE ARE THE SHORT PIECES OF DNA IN THIS CASE; THAT'S WHAT "DEOXYRIBO" MEANS -- "IN A MOLAR EXCESS OF PRIMER; ITS COMPLEMENTARY STRAND, UNDER CONDITIONS SUCH THAT AN

EXTENSION PRODUCT OF EACH PRIMER IS SYNTHESIZED" BY "E. COLI DNA POLYMERASE 1 . . ."

SO THE PRIMERS ARE ADDED (INDICATING), AND THE EXTENSION PRODUCT, PRIMER EXTENSION, IS DONE WITH:

". . . E. COLI DNA POLYMERASE 1 OR KLENOW FRAGMENT THEREOF, WHICH EXTENSION PRODUCT IS COMPLEMENTARY TO EACH STRAND."

SO THE EXTENSION PRODUCT AGAIN (INDICATING). UNFORTUNATELY, WE CAN'T ADD THESE UNITS ONE-BY-ONE. BUT YOU REMEMBER THAT THE DNA POLYMERASE IS A LITTLE MACHINE THAT ADDS EACH UNIT ONE-BY-ONE, TAKING ITS DIRECTION FROM THE TEMPLATE TO PRODUCE TWO MOLECULES OF THE ORIGINAL STARTING TEMPLATE.

SO WHERE ARE WE? THIS WORDING GETS A LITTLE TEDIOUS.

". . . WHEREIN SAID PRIMERS ARE SELECTED SO AS TO BE SUFFICIENTLY COMPLEMENTARY TO DIFFERENT STRANDS OF EACH SPECIFIC SEQUENCE TO HYBRIDIZE THEREWITH SUCH THAT THE EXTENSION PRODUCT SYNTHESIZED FROM ONE PRIMER, WHEN IT IS SEPARATED FROM ITS COMPLEMENT, CAN SERVE AS A TEMPLATE FOR SYNTHESIS OF THE EXTENSION PRODUCT OF THE OTHER PRIMER."

THIS IS JUST LANGUAGE WHICH IT'S DESIGNED TO EXPLAIN WHERE THE PRIMERS ARE GOING TO BE ON THE TEMPLATES RELATIVE TO EACH OTHER, AND THAT THE PRIMER EXTENSION PRODUCT CAN -- CAN THEN SERVE -- THIS IS THE PRIMER EXTENSION PRODUCT NOW (INDICATING) -- CAN -- CAN SERVE AS A TEMPLATE FOR A SUBSEQUENT

ROUND.

AND, SIMILARLY, THIS PRIMER EXTENSION PRODUCT (INDICATING) CAN SERVE AS A TEMPLATE FOR A SUBSEQUENT ROUND. THAT'S OBVIOUS BECAUSE THE TWO -- TWO STRANDS ARE IDENTICAL TO THE STARTING DNA.

SO NOW WE'VE GONE THROUGH ONE ROUND OF PRIMER EXTENSION. YOU THEN:

SEPARATE "THE PRIMER EXTENSION PRODUCTS FROM THE TEMPLATES ON WHICH THEY ARE SYNTHESIZED TO PRODUCE SINGLE-STRANDED MOLECULES" --

LIKE HERE (INDICATING).

-- "BY PHYSICAL, CHEMICAL OR ENZYMATIC MEANS" --

AGAIN RECITING WHAT'S IN STEP (A). SO YOU HAVE TO -- YOU SEPARATE THEM. PHYSICAL METHODS WOULD INCLUDE HEATING. YOU HEAT THEM.

AND THEN "TREATING THE SINGLE-STRANDED MOLECULES GENERATED FROM STEP (C) WITH TWO PRIMERS OF STEP (B), IN A MOLAR EXCESS OF PRIMER; ITS COMPLEMENTARY MOLECULE, UNDER CONDITIONS SUCH THAT A PRIMER EXTENSION PRODUCT IS SYNTHESIZED, USING E. COLI DNA POLYMERASE 1 OR KLENOW FRAGMENT THEREOF, AND USING EACH OF THE SINGLE STRANDS PRODUCED IN STEP (C) AS TEMPLATES."

SO THIS STRAND CAN BE -- CAN SERVE AS . . . AS A TEMPLATE (INDICATING), AND THIS STRAND CAN SERVE AS A TEMPLATE

(INDICATING), TO PRODUCE -- OR THIS ONE (INDICATING), TO PRODUCE FOUR MOLECULES NOW STARTING WITH TWO MOLECULES -- ONE MOLECULE.

SO YOU START WITH A NUCLEIC -- DOUBLE-STRANDED NUCLEIC ACID. YOU DUPLICATE IT, AND THEN YOU DUPLICATE IT AGAIN.

Q. THANK YOU, DOCTOR.

DOCTOR, CAN YOU EXPLAIN WHETHER OR NOT YOU BELIEVE THAT THE PROCESS DESCRIBED IN CLAIM 19 IS TAUGHT IN DR. KHORANA'S PRIOR ART. AND I'VE PLACED THE NSF GRANT APPLICATION UP HERE FOR YOUR CONVENIENCE.

A. OKAY. WELL, YES, I WOULD SAY THIS IS THE PROCESS.

YOU START WITH A DOUBLE-STRANDED DNA; OKAY? AS UP HERE, IT SAYS YOU . . . YOU START WITH A DOUBLE-STRANDED DNA.

YOU DENATURE THE BIHELICAL STRUCTURE IN THE PRESENCE OF AN EXCESS OF TWO APPROPRIATE PRIMERS.

SO HERE YOU SEPARATE THE STRANDS OF THE DNA (INDICATING), WHICH IS DENATURATION.

TWO, YOU REPAIR THE -- REPAIR IN THE PRESENCE OF THE ENZYMES SO AS TO COMPLETE THE DOUBLING OF THE ORIGINAL COMPLEX DUPLEX.

THAT'S WHAT STEP (B) COMPRISES.

AND THEN THREE. REPEAT THE DENATURATION OF THE WHOLE CYCLE.

STEP (C) AND D IS DENATURATION AND ANOTHER CYCLE.

YOU NOTICE YOU'RE NOT ADDING ADDITIONAL. IT'S THE SAME PRIMERS IN THIS -- IN THIS PARTICULAR CASE.

SO ONE MOLECULE GOES TO TWO, AND TWO MOLECULES GOES TO FOUR.

Q. THANK YOU, DOCTOR.

A. (WITNESS RESUMES WITNESS STAND.)

MR. FIGG: YOUR HONOR, I'M ABOUT TO SWITCH TO A DIFFERENT PATENT. MIGHT THIS BE THE APPROPRIATE TIME FOR OUR RECESS?

THE COURT: RIGHT ON TIME, IT LOOKS LIKE.

(LAUGHTER)

THE COURT: OKAY. THEN WE'LL SEE YOU TOMORROW AT SOME TIME AFTER 12:30. BUT, AS I SAID, EITHER AWAIT SOMEONE TO BRING YOU OVER. ONE OF MY LAW CLERKS OR SOMEONE ELSE WILL COME OVER AND GET YOU, OR THE MARSHAL, DEPENDING UPON WHAT THE SITUATION IS. AND I TRUST BY THAT TIME, IT WILL HAVE QUIETED DOWN.

SO 12:30 AT OPERA PLAZA, AND THEN OVER HERE, AND WE'LL GET STARTED AS SOON AS WE CAN AND RECESS AT 3:30.

PLEASE FOLLOW THE INSTRUCTIONS I'VE GIVEN YOU ABOUT NOT DISCUSSING THE CASE AMONGST YOURSELVES OR WITH ANYONE ELSE.

YOU MAY STEP DOWN.

(WITNESS EXCUSED)

(JURY EXCUSED)

(OPEN COURT, JURY NOT PRESENT:)

THE COURT: COUNSEL, ARE THERE ANY OTHER MATTERS WE NEED TO TAKE UP NOW, OR ARE WE . . .

MR. FIGG: NOT AT THE MOMENT.

YOUR HONOR, WE DO HAVE A PROTECTIVE ORDER -- WE'VE SIGNED THIS NOW --

MR. PASAHOW: OKAY.

MR. FIGG: -- THAT ALL COUNSEL HAVE AGREED TO, INCLUDING COUNSEL FOR THE CITY OF HOPE, WITH RESPECT TO SOME DOCUMENTS THAT DR. WALLACE PRODUCED -- OR I SHOULDN'T SAY DR. WALLACE -- THE CITY OF HOPE PRODUCED --

THE COURT: UH-HUH.

MR. FIGG: -- TO CETUS IN RESPONSE TO A SUBPOENA.

THE COURT: UH-HUH. NOW, NONE OF THOSE HAVE BEEN INTRODUCED INTO EVIDENCE SO FAR.

MR. FIGG: THEY HAVE NOT BEEN INTRODUCED INTO EVIDENCE. WE HAVE JUST RECENTLY REVIEWED THEM.

WE ARE GOING TO HAVE SOME OBJECTIONS TO THEIR USE --

THE COURT: UH-HUH.

MR. FIGG: -- TO THE RELEVANCY OF THEM, BUT I THINK IT MAY BE MORE APPROPRIATE TO TAKE THAT UP WHEN THE TIME COMES.

THE COURT: YOU INTEND TO USE THEM DURING CROSS ON -- OF DR. WALLACE?

MR. PASAHOW: YES, YOUR HONOR.

THE COURT: ARE THE OBJECTIONS GOING TO BE PRETTY MUCH THE SAME, RELATING TO ALL THE DOCUMENTS --

MR. FIGG: THEY ARE.

THE COURT: -- TO WHICH YOU HAVE OBJECTIONS?

MR. FIGG: THEY ARE, YOUR HONOR. WE -- MAYBE WE SHOULD

GET INTO IT NOW. I DON'T KNOW. WE --

THE COURT: WELL, HOW MUCH -- HOW MUCH FOUNDATIONAL OR UNDERLYING TESTIMONY AM I GOING TO NEED TO HEAR IN ORDER TO RESOLVE IT?

MR. FIGG: PERHAPS NONE. THE -- I DON'T THINK THERE'S ANY DISAGREEMENT ABOUT WHAT THE DOCUMENTS ARE.

THE CITY OF HOPE HAS FILED PATENT APPLICATIONS IN THE NAME OF DR. WALLACE AND OTHERS, OTHERS OF DR. WALLACE'S CO-WORKERS --

THE COURT: UH-HUH.

MR. FIGG: -- AND THE CITY OF HOPE IS PROSECUTING THESE PATENT APPLICATIONS IN THE PATENT & TRADEMARK OFFICE. SOME OF THEM EMPLOY AMPLIFICATION TECHNIQUES AND REFER TO THE . . . THE PCR REACTION.

AND IT'S OUR UNDERSTANDING, ALTHOUGH WE DON'T KNOW EXACTLY WHAT CETUS INTENDS TO DO WITH THEM, THAT CETUS PLANS TO REFER TO SOME OF THE STATEMENTS DR. WALLACE'S ATTORNEYS OR CITY OF HOPE'S ATTORNEYS MADE TO THE PATENT OFFICE IN CONNECTION WITH THE PATENTABILITY OF WHAT IS CLAIMED IN THOSE PATENTS AND SOMEHOW ARGUE THAT THAT'S INCONSISTENT WITH DR. WALLACE'S TESTIMONY HERE.

YOU MIGHT RECALL THAT WE HAD A SOMEWHAT SIMILAR ARGUMENT IN CONNECTION WITH THE EUROPEAN PROSECUTION OF THE CETUS PATENT, AND YOUR HONOR RULED THERE THAT PROSECUTION OF A DIFFERENT PATENT APPLICATION IN A DIFFERENT COUNTRY WOULD -- WAS

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NOT RELEVANT TO THE QUESTION OF PATENTABILITY HERE.

WE WOULD SIMILARLY ARGUE THAT THE ARGUMENTS DR. WALLACE MAKES OR HIS ATTORNEYS MAKE TO THE PATENT OFFICE IN CONNECTION WITH A DIFFERENT INVENTION CLAIMED IN A DIFFERENT PATENT APPLICATION REALLY HAS NO BEARING ON THE QUESTION OF WHETHER THE CLAIMS IN THE '202 AND THE '195 PATENTS ARE VALID.

AND THAT WILL BE THE -- IN ESSENCE, THE BASIS OF OUR REJECTION -- OBJECTIONS.

THE COURT: WELL, THE MAJOR -- THE MAJOR DIFFERENCE, AND REALLY WHAT WAS CRITICAL WITH RESPECT TO THE RULING IN YOUR CASE, WAS THE FACT THAT THESE WERE PATENTS THAT WERE PROSECUTED IN FOREIGN COUNTRIES WHERE WE'D ESSENTIALLY HAVE TO GET INTO THE NATURE OF THE LAWS AND RULES AND STATUTES AND SO FORTH, AND SO WE'RE REALLY NOT OPERATING UNDER THE SAME RULES.

IS -- IS DR. WALLACE THE NAMED INVENTOR ON THE PATENT OR PATENTS IN QUESTION?

MR. FIGG: MOST OF THEM, IF NOT ALL OF THEM HE, IS A CO-INVENTOR.

THE COURT: UH-HUH.

MR. FIGG: THERE ARE SEVERAL OTHER NAMED INVENTORS.

THE COURT: UH-HUH. AND CITY OF HOPE IS THE ASSIGNEE?

MR. FIGG: THAT'S MY UNDERSTANDING, YES.

MR. PASAHOW: YES, YOUR HONOR, THAT'S CORRECT.

THE COURT: UH-HUH. UH-HUH.

MR. PASAHOW: AS TO THE STATEMENTS WE INTEND TO USE,

DR. WALLACE HAS SWORN UNDER THE STATUTORY PENALTY THAT THEY'RE TRUE AND CORRECT.

THE COURT: ARE THESE STATEMENTS THAT DR. WALLACE HIMSELF HAS MADE WITH RESPECT TO THE PATENT?

MR. PASAHOW: THEY ARE STATEMENTS THAT ARE CONTAINED IN THE PATENT APPLICATIONS THAT HE HAS VERIFIED.

THE COURT: UH-HUH.

MR. FIGG: WELL, THAT'S HELPFUL, IF THEY ARE STATEMENTS MADE IN THE PATENT APPLICATIONS. I HAD UNDERSTOOD THAT CETUS PLANNED TO USE STATEMENTS MADE DURING ARGUMENTS TO THE PATENT & TRADEMARK OFFICE.

THE COURT: WELL, I THINK -- OBVIOUSLY, YOU HAVE TO LAY A FOUNDATION FOR THEM. EITHER THEY'RE HIS STATEMENTS OR STATEMENTS WERE ADOPTED BY HIM AND, ESSENTIALLY, THEREFORE, HE HAD TO HAVE KNOWN OF THEM, IF NOT VERIFIED THEM HIMSELF, AND KNOWN THAT THEY WERE BEING MADE IN BEHALF OF THE PATENT, AND ESSENTIALLY SOME FORM OF ADOPTION OR RATIFICATION.

BUT IF IT'S WHAT HE'S VERIFIED, THEN, THEN I THINK YOU'RE ENTITLED TO GO INTO IT, IF THEY'RE INCONSISTENT.

MR. PASAHOW: (NODDING HEAD.)

THE COURT: OKAY. WELL, WITH THAT UNDERSTANDING, THEN --

MR. FIGG: WELL, WHEN WE SEE THE PARTICULAR STATEMENTS THAT CETUS PLANS TO USE, THEN WE'D LIKE TO HAVE AN OPPORTUNITY TO AT LEAST THINK ABOUT RENEWING OUR MOTION WITH RESPECT TO THE

RELEVANCY OF THOSE PARTICULAR STATEMENTS, BECAUSE THE PROBLEM WE HAVE HERE IS, IF YOU'RE CLAIMING ONE INVENTION AND YOU THINK IT'S PATENTABLE, THAT MAY OR MAY NOT HAVE ANY RELEVANCE AT ALL TO WHETHER A TOTALLY DIFFERENT INVENTION IS PATENTABLE.

SO I THINK WE PROBABLY HAVE TO --

THE COURT: WELL, IT WOULD SEEM TO ME IT'S NOT A QUESTION OF PATENTABILITY AND WHAT YOU THINK ABOUT THAT BUT RATHER OF WHETHER OR NOT THE STATEMENTS IN TERMS OF THE SCIENCE AND TECHNOLOGY THAT IS -- THAT IS CLAIMED OR REFERRED TO IS -- THOSE STATEMENTS ARE INCONSISTENT WITH STATEMENTS THAT ARE MADE HERE.

MR. FIGG: YES, I WOULD AGREE WITH THAT. IF -- IF HE'S MAKING STATEMENTS OF FACT OR OPINION ABOUT TECHNOLOGY, THAT'S ONE THING.

THE COURT: UH-HUH.

MR. FIGG: IF HE'S SIMPLY SAYING, "I'VE MADE THIS INVENTION" OR "I AND SEVERAL OTHER PEOPLE HAVE MADE THIS INVENTION, AND WE'D LIKE THE PATENT OFFICE TO CONSIDER WHETHER IT'S PATENTABLE OR NOT," THAT HAS VERY LITTLE RELEVANCE TO WHETHER THE SUBJECT MATTER CLAIMED HERE IS PATENTABLE.

MR. PASAHOW: WELL, YOUR HONOR --

THE COURT: YES.

MR. PASAHOW: -- TO SOME EXTENT, IT GETS TO BE MUCH LIKE THIS CLAIM IN CLAIM 14. THE THINGS THAT AREN'T SO OBVIOUS TO ONE ORDINARILY SKILLED IN THE ART, ACCORDING TO MR. WALLACE'S

TESTIMONY, FROM GOING FROM THE KLEPPE MATERIAL TO PCR, ARE -- ARE RADICALLY GREATER THAN THE DIFFERENCES OF THE MATTERS AS TO WHICH HE IS CLAIMING THAT HE IS AN INVENTOR OF A NEW AND NOVEL PROCESS IN SOME OF THESE PATENTS.

THE COURT: UH-HUH.

MR. FIGG: WELL, AGAIN, I -- SINCE I DON'T KNOW PRECISELY WHAT MR. PASAHOW HAS IN MIND, I THINK WE'LL HAVE TO DEAL WITH THAT AS IT COMES UP.

THE COURT: WE'LL HAVE TO SEE WHAT THE PARTICULAR AREAS ARE THAT YOU'RE GOING TO EXAMINE HIM ON. OKAY.

MR. PASAHOW: I --

MR. FIGG: BUT, IN ANY EVENT, WE DO HAVE A PROTECTIVE ORDER HERE WHICH WE'VE EACH SIGNED.

THE COURT: OKAY. FINE. THEN I'LL SIGN OFF ON IT.

MR. PASAHOW: I THINK YOUR HONOR WILL WANT TO READ IT CAREFULLY BECAUSE, AT THE REQUEST OF THE CITY OF HOPE ATTORNEYS, WE HAVE LEFT IN THE PROVISIONS WHICH I BELIEVE GO SO FAR AS TO REQUIRE EXCLUSION FROM THE COURTROOM.

THE COURT: I SEE. WELL . . .

YOU'RE NOT SUGGESTING, MR. PASAHOW, THAT I MAY SIGN THINGS WITHOUT READING THEM CAREFULLY; ARE YOU?

(LAUGHTER)

(PAUSE IN PROCEEDINGS)

MR. FIGG: INCIDENTALLY, YOUR HONOR, COUNSEL FOR CITY OF HOPE IS MR. ED IRONS, WHO HAS JUST STEPPED FORWARD, SO IF YOU

HAVE ANY PARTICULAR QUESTIONS ABOUT CITY OF HOPE, HE WOULD BE THE PERSON TO ANSWER THEM.

(PAUSE IN PROCEEDINGS)

THE COURT: WELL, IT WOULD APPEAR, UPON A QUICK PERUSAL, THAT THE ONLY -- THE ONLY PARAGRAPH THAT PRESENTS ANY PROBLEM IS PARAGRAPH 7, AND THE REST OF IT HAS TO DO WITH THE MATERIALS AND THEIR USE AND THEN THE SEALING OF THEM, BUT . . .

AND I SUPPOSE, YOU KNOW, THERE'S NOTHING WRONG WITH A PARTY REQUESTING THE COURT TO MAKE ARRANGEMENTS, BUT I ADVISE YOU THAT THE COURT WILL NOT MAKE SUCH ARRANGEMENTS, BECAUSE I WILL NOT CLOSE THE COURTROOM.

AND, YOU KNOW, I WILL CERTAINLY AGREE TO AN ORDER SEALING DOCUMENTS AND MAKING THEM AVAILABLE ONLY WHEN NECESSARY TO QUALIFIED PERSONS AND, OF COURSE, YOU KNOW, TO THE JURY AND COURT DURING THE COURSE OF THESE PROCEEDINGS.

BUT I'M NOT GOING TO CLOSE THE COURTROOM TO ONLY, QUOTE, "QUALIFIED PERSONS." I JUST WON'T DO THAT. THAT'S -- IT'S A PUBLIC FORUM, AND HAD -- HAD THE CITY OF HOPE FELT THAT STRONGLY ABOUT IT, THEN IT SHOULDN'T HAVE ALLOWED ITS -- YOU KNOW, ONE OF ITS SCIENTISTS OR DOCTORS TO TESTIFY, I SUPPOSE, BUT -- YES?

MR. IRONS: MAY I COMMENT, PLEASE, YOUR HONOR?

THE COURT: YES.

MR. IRONS: MY NAME IS EDWARD IRONS, SPELLED I-R-O-N-S. I AM COUNSEL FOR THE CITY OF HOPE.

I DID NOT DRAFT THIS PROPOSED PROTECTIVE ORDER. THE CITY OF HOPE DOES NOT INSIST UPON PARAGRAPH 7.

THE COURT: UH-HUH.

MR. IRONS: IT IS NOT IN ISSUE.

MR. FIGG: OKAY.

THE COURT: WHERE DID PARAGRAPH 7 COME FROM, THEN?

MR. IRONS: I SHALL NOT COMMENT, BUT I DID NOT -- IT DID NOT COME FROM ME.

(LAUGHTER)

THE COURT: WELL, THEN, WHY DON'T WE JUST STRIKE IT?

MR. IRONS: I AGREE.

MR. PASAHOW: VERY GOOD, YOUR HONOR.

THE COURT: FINE. OKAY. THEN NO ONE WILL HAVE TO BE IN THE POSITION OF REQUESTING, AND I WON'T HAVE TO BE IN THE POSITION OF DENYING, HAVING ALREADY DONE SO, I GUESS, IN ESSENCE.

SO PARAGRAPH 7 IS DELETED AND THE COURT WILL SIGN -- I LOOKED THROUGH IT VERY QUICKLY, AND I -- I WILL READ THE REST OF IT BEFORE I SIGN IT, BUT IT APPEARED TO ME THAT'S THE ONLY AREA WHERE IT SHOWED UP; IS THAT CORRECT?

MR. PASAHOW: I BELIEVE THAT'S RIGHT, YOUR HONOR.

THE COURT: OKAY. FINE. THEN THAT -- THAT WILL BE FILED THIS AFTERNOON. I JUST WANT TO GO OVER IT IN GREATER DETAIL.

ANYTHING FURTHER?

MR. FIGG: NO, YOUR HONOR.

MR. PASAHOW: NO, YOUR HONOR.

THE COURT: THEN WE'LL SEE YOU TOMORROW.

MR. PASAHOW: HOPEFULLY.

THE COURT: YES. I TRUST SO.

(COURT ADJOURNED AT 1:14 P.M. TO RECONVENE TUESDAY, JANUARY 15, 1991, AT 12:30 P.M.)