THEY'LL BE OUT THERE IN LITTLE BUNCHES.

AND THAT TIME, THE TIME THAT IT TAKES FOR THAT TO HAPPEN, TO SOME -- TO A CERTAIN -- LIKE THE TIME THAT IT TAKES FOR 90 PERCENT OF THEM TO HAVE DONE THAT WILL BE RELATED TO THE CONCENTRATION OF THEM; IN OTHER WORDS, THE NUMBER.

IF YOU HAVE -- IF YOU THROW TEN OF THEM OUT THERE, IT MAY TAKE A DAY OR TWO BEFORE THEY'LL HAVE FOUND EACH OTHER AND CLUMPED TOGETHER. IF YOU TAKE A HUNDRED, NOT -- MORE OF THEM WILL CLUMP TOGETHER FASTER. THERE'LL ALWAYS BE A FEW OF THEM THAT HAVEN'T AROUND, BUT 90 PERCENT OF THEM WILL HAVE CLUMPED TOGETHER IN A SHORTER TIME.

IF YOU JUST TOTALLY FILL THE WHOLE SURFACE OUT THERE WITH THOSE BAR MAGNETS, THEY WILL CLUMP TOGETHER EVEN FASTER.

NOW -- AND IT WON'T REALLY MATTER. IF YOU THINK OF THOSE BAR MAGNETS AS THE TEMPLATE, OKAY, THEY MAKE A STRONG ATTACHMENT TO EACH OTHER.

THE TEMPLATES, SEE, THEY DO ATTRACT EACH OTHER BY A SIMILAR KIND OF FORCE. IT'S LIKE THE ELECTROMAGNETIC STUFF THAT STICKS THE TWO TEMPLATES BACK TOGETHER, AND THE LONGER THE TEMPLATE -- THE LONGER THE TEMPLATE IS, THE STRONGER THE BOND WILL BE, JUST LIKE IF YOU HAVE A REALLY BIG BAR MAGNET, IT'LL HOLD ANOTHER BAR MAGNET UP BESIDE IT MUCH TIGHTER THAN A LITTLE ONE.

IF YOU THINK OF THE PRIMERS AS BEING LITTLE BAR MAGNETS ALSO FLOATING AROUND ON THE SURFACE OF THE SWIMMING POOL, THEY

ALSO HAVE A TENDENCY TO CLUMP ON TO THE ENDS OF THE BIG BAR MAGNETS. THEY WON'T BIND QUITE SO TIGHTLY, BUT THEY WILL WANT TO.

BUT IF -- ONCE TWO BIG BAR MAGNETS ARE STUCK TOGETHER, A LITTLE TEENY ONE IS NOT GOING TO BE ABLE TO GET IN THERE AND FORM A -- IT'LL JUST GET KICKED OFF.

SO WHEN YOU'RE DESIGNING A REACTION WHERE YOU'RE -- THERE'S A COMPETITION BETWEEN THE LITTLE BAR MAGNETS THAT DON'T HAVE A PRAYER, IF YOU WAIT LONG ENOUGH -- AND THE BIG BAR MAGNETS, YOU DON'T WANT TO WAIT TOO LONG. YOU CAN THROW A HANDFUL OF BAR MAGNETS OUT THERE, POUR IN A WHEELBARROW FULL OF LITTLE BAR MAGNETS, AND IF YOU'RE QUICK, YOU CAN GET THE LITTLE BAR MAGNETS EXTENDED ON THE BIG ONES. IF WE WERE TALKING MOLECULES AGAIN, BEFORE THE BIG ONES KNOCK THE LITTLE ONES OFF AND COME BACK TOGETHER.

BUT IF YOU -- IF YOU THROW A WHEELBARROW FULL OF BIG ONES IN THERE IN THE FIRST PLACE, THEN YOU HAVE TO BE EVEN QUICKER IF YOU'RE GOING TO EXPECT THE BIG BAR MAGNETS TO -- THE LITTLE BAR MAGNETS TO BE THERE WHEN YOU COME IN WITH YOUR ENZYME.

IF YOU WAIT TOO LONG, THERE'S JUST NO WAY THAT THE LITTLE PRIMERS ARE GOING TO HAVE A CHANCE TO BE EXTENDED ON THE BIG PIECES OF DNA. IF YOU HAVE -- AND THE MORE CONCENTRATED THE DNA IS, THE QUICKER YOU HAVE TO BE.

SO THERE'S SOME -- THERE'S SOME LIMITS IN THERE WHEN

YOU -- IF YOU HAVE A REALLY REALLY CONCENTRATED SOLUTIONS, IT DOESN'T WORK AT ALL.

Q. NOW, IF YOU HAVE A LOT OF THESE BAR MAGNETS OR A LOT OF TEMPLATE IN A SOLUTION AND YOU WAIT A LONG TIME, CAN YOU TAKE CARE OF THE PROBLEM BY INCREASING THE NUMBER OF LITTLE MAGNETS OR PRIMERS YOU PUT IN?

A. YOU REALLY CAN'T, BECAUSE IT'S LIKE -- BACK TO THE BAR MAGNET BUSINESS:

IF YOU -- IT DOESN'T MATTER HOW MANY OF THE LITTLE ONES THERE ARE. IF THE BIG ONES HAVE HAD ENOUGH TIME TO FIND EACH OTHER, THEY'RE GOING TO BE CLUMPED TOGETHER, AND THEY'RE NOT GOING TO COME UNCLUMPED JUST BECAUSE THERE'S A BUNCH OF LITTLE ONES OUT THERE THAT WOULD BE THERE IF THE BIG ONES WEREN'T.

IT'S LIKE THE FORCE THAT DRIVES THE -- THE LONG TEMPLATES BACK TOGETHER IS VERY STRONG COMPARED TO THE FORCE THAT ALLOWS THE LITTLE PRIMERS TO STICK TO IT.

AND SO ONCE YOU FORMED THE ORIGINAL DUPLEX AGAIN, ONCE THE TEMPLATES RENATURED, YOU ARE NOT GOING TO BE ABLE TO GET PRIMING.

AND IT DOESN'T MATTER HOW MANY PRIMERS YOU DUMP IN THERE. YOU CAN DUMP IN A MILLION-FOLD EXCESS OF PRIMERS. IF YOU WAIT LONG ENOUGH FOR THE TEMPLATE TO REASSOCIATE, YOU STILL ARE NOT GOING TO GET PRIMER EXTENSION ON THAT TEMPLATE.

Q. DO YOU ALSO HAVE UP THERE THE FILING WE'VE BEEN CALLING THE NATIONAL SCIENCE FOUNDATION GRANT, EXHIBIT A-17?

A. YES. LET'S SEE.

I DO.

Q. WHEN DID YOU FIRST SEE THAT?

A. I GUESS A MONTH OR TWO AGO, MAYBE TWO MONTHS AGO.

Q. DOES THAT NATIONAL SCIENCE FOUNDATION GRANT HAVE WITHIN IT A DESCRIPTION OF CONDITIONS THAT COULD BE USED FOR THE PCR PROCESS?

A. THERE ARE NO -- THERE AREN'T ANY EXPERIMENTAL CONDITIONS GIVEN IN THIS, AS FAR AS I CAN TELL. I MEAN . . . THAT -- I MEAN, IT'S A LOT OF -- THERE'S A LOT OF SORT OF -- THERE ARE SOME WORDS IN HERE, BASICALLY, BUT THERE ARE NO EXPERIMENTAL CONDITIONS.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) NOW, MR. FIGG SHOWED US EARLIER A GRAPH FROM A PAPER YOU HAD DONE, AND I'D LIKE TO GET YOU TO EXPLAIN IT, IF YOU COULD.

THIS IS THE GRAPH.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) DO YOU RECALL THIS GRAPH?

A. YES. IT WAS A VERY PLEASANT EXPERIMENT.

Q. WHAT WAS THE EXPERIMENT THAT PRODUCED THAT GRAPH?

A. IT WAS -- IT WAS ONE IN WHICH WE -- WE TOOK A PLASMID, STARTED WITH A PLASMID, AND WE WERE GOING -- WE AMPLIFIED A 109-BASE PAIR, OR 110-BASE PAIR, I THINK, FRAGMENT OUT OF IT. AND WHAT WE DECIDED TO DO WAS LOOK AT WHAT HAPPENED AFTER EVERY

CYCLE.

SO WE RAN THE TEN CYCLES AND TOOK ALIQUOTS -- I THINK WE'VE HAD THAT WORD. WE TOOK SAMPLES OUT OF THEM AFTER EVERY CYCLE.

AND WE HAD INCLUDED IN THE REACTION A RADIOACTIVE TRACER, EVEN THOUGH AT THIS POINT WE WERE ABLE TO -- WE WERE ABLE TO MAKE ENOUGH DNA FRAGMENT THAT WE COULD SEE IT WITHOUT THE TRACER. BUT WHAT WE WANTED TO DO IN THIS EXPERIMENT IS QUANTITATE IT, AND SO WE PUT A TRACER IN.

WE PUT A LITTLE -- THE C -- PUT A RADIOACTIVE C IN THE SOLUTION, AND SO AS THE FRAGMENTS WERE GETTING MADE, THEY -- THEY WERE RADIOACTIVELY-LABELED.

AND SO WE COULD -- WE COULD TAKE THE -- THE SAMPLES FROM THE FIRST CYCLE, SECOND CYCLE, THIRD CYCLE, AND SO FORTH, PUT THEM ON A GEL, JUST ON THE -- LINED UP ON THE TOP, RUN THE GEL.

AND THEN WITH THE ULTRAVIOLET LIGHT AND THE PHYTIN BROMIDE, WE COULD SEE THE 110-BASE PAIR BAND WE HAD MADE, AND WE COULD CUT IT OUT WITH A RAZOR BLADE, JUST CUT IT OUT OF THE GEL, AND DROP THE LITTLE PARTS THAT WERE THE BAND INTO A LITTLE TUBE FULL OF WATER AND COUNT IT IN A SCINTILLATION COUNTER.

AND SO THAT'S WHAT'S PLOTTED. THE COUNTS ACTUALLY IS NOT PLOTTED ON THE AXIS, THE VERTICAL AXIS. THAT'S THE COUNTS MULTIPLIED BY SOME NUMBER THAT WOULD TELL YOU HOW MANY PICOMOLES WERE IN A THOUSAND COUNTS, OR SOMETHING LIKE THAT. SO IT'S

DIRECTLY RELATED TO COUNTS.

SO WE'RE PLOTTING THE AMOUNT OF MATERIAL THAT IS CONVERTED FROM MONONUCLEOTIDES, FROM THESE LITTLE BUILDING BLOCK ELEMENTS THAT ARE RADIOACTIVE, INTO THE 110-BASE PAIR FRAGMENTS THAT WE'RE AMPLIFYING AS A FUNCTION OF MORE CYCLES, SO WE GOT THAT.

AND WE TOOK THAT -- WE TOOK THOSE NUMBERS, PUT THEM IN A COMPUTER WITH A CURVE FITTING PROGRAM THAT WOULD SAY WHAT IS THE YIELD EVERY CYCLE IF THIS IS AN EXPONENTIAL PROCESS THAT IS CAUSING THESE NUMBERS, AND THE PROGRAM'S AT SOMETHING LIKE 64 PERCENT OR SOMETHING LIKE THAT.

THAT'S WHERE THAT CURVE COMES FROM. WE DIDN'T DRAW THE CURVE TO GO THROUGH THE POINTS. THE COMPUTER DROVE -- DREW THE CURVE AS IT THEORETICALLY WOULD BE, AND THAT'S THE BEST EXPONENTIAL FIT.

IT'S LIKE . . . DOES THAT . . .

Q. NOW, WE'VE HEARD TESTIMONY, AND YOU'VE HEARD IT AS WELL, ABOUT EXPERIMENTS THAT WERE DONE IN DR. KHORANA'S LABORATORY WHERE THEY WERE MEASURING THE RADIOACTIVITY OF DNA THAT WAS BEING INCORPORATED.

WAS THAT THE SAME THING THAT YOU DID HERE?

A. WELL, WHAT THEY WERE DOING WAS, THEY WERE TAKING TOTAL RADIOACTIVITY THAT WAS BEING TURNED INTO SOMETHING BESIDES THE NUCLEOTIDE, BASICALLY, THAT HAD PROPERTIES LIKE DNA.

THEY WERE NOT PUTTING IT ON A GEL, SEPARATING OUT WHAT

THEY THOUGHT THEY WERE GOING TO SEE, AND JUST LOOKING AT THE RADIOACTIVE ASSOCIATED WITH THAT. THEY WERE LOOKING AT ALL OF THE RADIOACTIVITY THAT GOT CONVERTED FROM THE NUCLEOTIDES THAT THEY HAD PUT IN THERE INTO SOMETHING THAT WOULD HAVE PROPERTIES LIKE DNA. THAT COULD HAVE BEEN A LOT OF DIFFERENT THINGS.

AND THEY WOULD NEVER HAVE GOTTEN AWAY WITH THAT KIND OF DATA AT CETUS. I MEAN, PEOPLE THERE WOULDN'T HAVE -- THEY WERE -- IF YOU'RE DEVELOPING A NEW PROCESS, LIKE I WAS DOING THERE, I WANTED TO SHOW FOR SURE THAT I WAS GETTING AN EXPONENTIAL ACCUMULATION OF THAT 110-BASE PAIR PRODUCT THAT I WAS SAYING I WAS MAKING.

AND I COULD SEE IT ON THE GEL. BY THEN, I KNEW I WAS GOING TO GET THE RIGHT NUMBERS BECAUSE I COULD SEE THE PRODUCT ACCUMULATING.

I MEAN, THIS -- THIS PICTURE IS ACCOMPANIED IN THAT ARTICLE, I THINK, BY A PICTURE OF THE GEL AND ALSO BY AN ANALYSIS OF THE FRAGMENTS THAT CAME OUT OF THE -- OUT OF THE 110 BASE PAIRS.

SO IT -- WE SORT OF NAILED IT DOWN WITH THIS EXPERIMENT. PEOPLE COULDN'T ARGUE WITH IT.

Q. NOW, IN -- WHEN YOU DID THIS EXPERIMENT AND YOU CUT SOME OF THE DNA FROM EACH CYCLE OUT OF THE GEL, WAS THERE OTHER RADIOACTIVE DNA THAT WAS BEING PRODUCED IN EACH OF THOSE CYCLES?

A. THE GEL -- THERE'S PLENTY OF RADIOACTIVITY ON THE GEL THAT WAS NOT COMING FROM OUR FRAGMENT. I MEAN, THERE WOULD HAVE BEEN

A LOT -- THERE'S ALWAYS RADIOACTIVITY UP AT THE ORIGIN, TREMENDOUS AMOUNT OF RADIOACTIVITY, IN FACT, UP THERE.

MOST OF THE RADIOACTIVITY IN THE EXPERIMENT WAS NOT GOING IN THE FRAGMENT. MOST OF IT'S JUST THE NUCLEOTIDES.

BUT VARIOUS OTHER THINGS WERE HAPPENING THAT WE . . . WE DIDN'T KNOW WHAT THEY WERE, BUT WE -- THAT'S WHY WE JUST WANTED TO CUT OUT OUR BAND AND SEE WHAT OUR PROCESS WAS DOING.

Q. IF YOU HAD COUNTED ALL OF THE RADIOACTIVITY THE WAY THAT THEY WERE DOING IN THE KHORANA LABORATORY, WOULD THAT HAVE CHANGED THE NUMBERS THAT ARE ON THIS CURVE?

A. IT WOULD HAVE. I CAN'T TELL YOU EXACTLY HOW IT WOULD HAVE CHANGED THEM. MY -- I KNOW THERE WAS A LOT OF STUFF ON -- THERE WAS A LOT OF RADIOACTIVITY ON THE GEL THAT WAS NOT ASSOCIATED WITH OUR BAND. IF WE'D HAVE JUST LUMPED ALL THAT TOGETHER, IT WOULD HAVE DEFINITELY CHANGED THE RESULTS.

Q. IT WOULD HAVE GIVEN YOU MUCH HIGHER NUMBERS?

A. IT WOULD HAVE GIVEN US MUCH HIGHER NUMBERS. IT MIGHT NOT HAVE BEEN AS NICE A CURVE, I MEAN.

Q. WHY DIDN'T YOU WANT TO USE THE HIGHER NUMBERS?

A. WELL, I WAS ONLY INTERESTED IN THE RADIOACTIVITY THAT I COULD PROVE CAME FROM THE FRAGMENT THAT I WAS HYPOTHESIZING THAT MY PROCESS WOULD PRODUCE.

I DIDN'T -- I MEAN, I COULD HAVE TAKEN THE WHOLE BOTTLE OF RADIOACTIVITY AND POURED IT IN THE COUNTER, BUT IT -- I MEAN, THIS IS THE WAY YOU DO, YOU KNOW, DEVELOPMENTAL KIND OF THING,

LIKE I WAS TRYING TO -- I WAS WORKING ON A BRAND NEW PROCESS AND I HAD TO PROVE TO MYSELF THAT IT REALLY DID WHAT I THOUGHT IT WAS GOING TO DO. AND I ALSO HAD TO PROVE TO THE GUYS DOWN THE HALL EVEN MORE.

AND IF I WAS GOING TO PUBLISH THIS LIKE I DID WITH THIS, I HAD TO DO IT IN A WAY THAT WOULD BE ACCEPTABLE TO THE REST OF THE SCIENTIFIC COMMUNITY. IT'S JUST LIKE -- IT'S JUST, YOU KNOW, GOOD RESEARCH STANDARD -- I MEAN, PRACTICE, WHATEVER YOU CALL IT. IT'S NOT BEING SLOPPY.

I MEAN, I WOULDN'T -- I WOULD BE SLOPPY, PROBABLY, MYSELF BUT, I MEAN, YOU JUST CAN'T GET AWAY WITH IT.

(PAUSE IN PROCEEDINGS)

THE WITNESS: THIS WAS A VERY PLEASANT EXPERIENCE TO DO THAT EXPERIMENT AND SEE IT REALLY COME OUT LIKE IT SHOULD. THAT WAS . . . IT WAS WORTH DOING THE WORK.

Q. (BY MR. PASAHOW) MR. FIGG HAS SHOWN US SEVERAL TIMES AN ARTICLE YOU WROTE, WHICH WAS MARKED AS EXHIBIT A-24, "THE POLYMERASE CHAIN REACTION: WHY IT WORKS."

ARE YOU FAMILIAR WITH THAT?

A. YES. I WROTE IT.

Q. AND YOU RECALL THAT IN THERE, YOU SAY:

"PCR IS AS SIMPLE TO PERFORM AS IT IS INTELLECTUALLY SATISFYING."

A. "TO CONTEMPLATE." "INTELLECTUALLY SATISFYING TO CONTEMPLATE."

YEAH. I SAY, "IT'S AS SIMPLE TO PERFORM AS IT IS INTELLECTUALLY SATISFYING TO CONTEMPLATE," AND I -- I BELIEVE THAT.

Q. WHAT DO YOU MEAN WHEN YOU SAY PCR IS SIMPLE?

A. WELL, IT'S SIMPLE TO DO IT. ONCE YOU HAVE THE PROTOCOLS IN HAND, WHICH YOU -- THEY'RE WIDELY AVAILABLE NOW.

I MEAN, ONCE I FIGURED OUT HOW TO DO IT, IT TURNED OUT IT WAS REAL EASY TO DO. IT'S NOT . . . I MEAN, IT'S A COMPLEX PROCESS, BUT ONCE YOU KNOW THE RULES, THEN IT'S NOT THAT HARD TO DO IT.

Q. IN THAT ARTICLE, YOU ALSO WROTE THAT:

"IT'S DIFFICULT TO FIND SITUATIONS IN WHICH PCR DOES NOT WORK."

WHAT DID YOU MEAN BY THAT?

A. IT MEANS THERE'S -- THERE'S NO SEQUENCES OR NO KINDS OF -- LIKE THERE'S NO CLINICAL SAMPLES I'VE TRIED TO ANALYZE, THERE'S NO PARTICULAR SEQUENCES THAT I'VE TRIED TO ANALYZE, WITH PCR WHERE I'VE HAD A PROBLEM GETTING IT TO WORK. I MEAN, SOMETIMES IT'S A LITTLE HARDER THAN OTHERS, BUT IT'S -- I'VE NO -- NOBODY HAS COME TO ME WITH A SEQUENCE THAT I CAN'T AMPLIFY, IS KIND OF WHAT I'M SAYING THERE.

Q. WELL, WE SAW SOME EXPERIMENTS YOU DID WHERE YOU DIDN'T GET PCR TO WORK.

A. WELL, THAT WAS WHEN I WAS TRYING TO GET IT -- THAT'S BEFORE I KNEW HOW TO DO IT.

I'M TALKING ABOUT ONCE I FIGURED OUT HOW TO DO IT, IT'S EASY TO GET IT TO WORK IN JUST ABOUT ANY CASE THAT SOMEBODY PRESENTS ME WITH.

THAT'S WHAT I DO FOR A LIVING. I GO TO OTHER COMPANIES, SHOW THEM HOW TO DO IT. I BASE THAT ON THE FACT THAT I DO KNOW HOW TO DO IT. I DON'T HAVE TO REINVENT IT EVERY TIME.

Q. NOW, BACK ON PAGE 241 OF THAT ARTICLE, YOU EXPLAIN THAT:

"TAQ IS USED NOT BECAUSE IT IS THE BEST POSSIBLE ENZYME FOR THE JOB BUT BECAUSE I SOMEWHAT ARBITRARILY PICKED IT FROM THE FOUR OR FIVE THERMOPHILIC ENZYMES THAT WERE DESCRIBED IN THE LITERATURE BY 1984."

THEN YOU GO ON: "WE FOUND IT WORKED OKAY FOR PCR AND NOBODY SAW FIT TO PURIFY ANY OTHERS."

NOW, FIRST OF ALL, COULD YOU EXPLAIN WHAT YOU MEAN IN THERE BY "THERMOPHILIC ENZYME"?

A. THE TERM MEANS HEAT LOVING. IT'S KIND OF A -- IT MEANS IT -- A THERMOPHILIC ENZYME IS NOT NECESSARILY A -- IT DOESN'T REALLY LOVE HEAT. IT DOESN'T GET DESTROYED BY HEAT IS WHAT THE MEANING OF THE TERM IS.

THEY COME FROM ORGANISMS GENERALLY CALLED THERMOPHILES, ALSO HEAT LOVING, THAT CAN STAND THE HEAT IN HOT SPRINGS AND STUFF LIKE THAT, OR WATER HEATERS. YOU CAN FIND THE THERMOPHILES IN WATER.

THE ENZYMES IN THEM HAVE TO BE ABLE TO STAND THE

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TEMPERATURES THAT THE ORGANISM LIVES IN. SO THEY'RE NOT EASILY DENATURED.

ALL OUR ORGANISMS LIVE IN OUR BODY TEMPERATURE, AND THEY AREN'T -- THEY JUST AREN'T BUILT TO STAND THE HIGHER TEMPERATURES. SO IF YOU HEAT A HUMAN BEING TO A HUNDRED DEGREES, IT KILLS THEM. IF YOU HEAT A THERMOPHILIC ENZYME TO A HUNDRED DEGREES, IT DOESN'T USUALLY KILL IT.

Q. ARE THERE OTHER THERMOPHILIC ENZYMES OTHER THAN THERMUS AQUATICUS WE'VE HEARD ABOUT?

A. THERE ARE LOTS OF THERMOPHILIC ORGANISMS. THERE ARE PROBABLY THOUSANDS OF THERMOPHILIC ORGANISMS. AND EVERY ORGANISM HAS TO HAVE A DNA POLYMERASE, AT LEAST ONE DNA POLYMERASE, SO THERE'S LOTS OF THEM.

Q. COULD THOSE OTHER POLYMERASES BE USED IN THE PCR PROCESS?

A. UNLESS THEY HAVE SOME NOXIOUS PROPERTY THAT PREVENT IT. MOST OF THEM PROBABLY HAVE PROPERTIES THAT ARE VERY SIMILAR TO THE ONES WE KNOW ABOUT, AND, YES, THEY COULD BE.

Q. WHEN DID YOU FIRST THINK OF USING A THERMOPHILIC ENZYME AS PART OF YOUR PCR PROCESS?

A. JUST ABOUT THE FIRST TIME THAT I REALIZED THAT I WAS GOING TO BE SITTING THERE IN THE LAB DOING SOMETHING OVER AND OVER AND OVER AGAIN, AND IT WOULD BE ADDING NEW ENZYME EVERY CYCLE.

AND I SAID, YOU KNOW WHAT? IF I HAD AN ENZYME THAT WOULDN'T DIE WHEN I HEATED, I WOULDN'T HAVE TO ADD IT. I WOULD NEVER HAVE TO OPEN THESE TUBES. ALL I'D HAVE TO DO IS TAKE A

RACK OF TUBES AND MOVE THEM FROM A HOT WATER BATH TO A COOLER PLACE AND BACK INTO THE HOT WATER. I WOULDN'T HAVE TO OPEN THE TUBES.

THAT WAS -- I WAS GETTING TIRED OF DOING THAT, SO IT WAS PRETTY EARLY ON. IT WAS RIGHT IN THE BEGINNING. IN FACT, WHEN I WAS JUST FIRST GETTING PCR TO WORK, I THOUGHT OF A WAY TO IMPROVE IT, YEAH.

Q. DID YOU USE A THERMOPHILIC ENZYME RIGHT AWAY?

A. I . . . I LOOKED UP ALL OF THE LITERATURE I COULD FIND ON THEM, AND CALLED AROUND TO THE ONES -- MOST OF THEM, UNFORTUNATELY, WERE PURIFIED. THE ONES IN THE LITERATURE WERE PURIFIED BY RUSSIANS, AND I DIDN'T KNOW THEIR PHONE NUMBERS. I DIDN'T EVEN KNOW HOW TO CALL RUSSIA BACK THEN.

BUT I CALLED THE ONES IN THE UNITED STATES. I SAID, "HEY, HAVE YOU GOT SOME OF THAT LEFT? WOULD YOU SEND ME A SAMPLE OF YOUR THERMO" -- NOBODY HAD ANY LEFT OR NOBODY WAS GOING TO GIVE ME ANY.

SO I TRIED TO GET SOME INTEREST GOING AT CETUS IN PURIFYING IT. I TRIED TO FIND SOMEBODY THERE TO PURIFY IT FOR ME. IT TOOK AWHILE BEFORE WE HAD IT, BUT FINALLY SOMEBODY DID.

Q. DO YOU STILL HAVE THAT SCIENTIFIC AMERICAN ARTICLE UP THERE? IT WAS EXHIBIT A-52.

A. YEAH. YES.

Q. DO YOU RECALL THAT, ON PAGE 64 OF THAT ARTICLE, YOU SAY THAT, AFTER SPENDING SOME MONTHS PREPARING FOR YOUR FIRST PCR

EXPERIMENT, YOU TRIED IT AND THE FIRST ONE WORKED?

A. I -- ACTUALLY, I DID SAY THAT IN THIS ARTICLE.

Q. WHY DID YOU WRITE --

A. I SELECTED --

Q. WHY DID YOU WRITE IN THE ARTICLE THAT THE FIRST EXPERIMENT WORKED?

A. WELL, WHEN I WROTE THIS ARTICLE, I HAD BEEN -- I HAD LEFT CETUS BY THEN MAYBE THREE YEARS, AND I WAS DOWN IN SAN DIEGO WHEN I WAS WRITING THIS.

AND I -- WHEN I LEFT CETUS, I HAD TO LEAVE ALL MY NOTEBOOKS AND STUFF THERE. THAT WAS -- THAT WAS THE PROPERTY OF CETUS.

AND, SEE, WHEN I WAS WRITING THIS, I DIDN'T HAVE THOSE TO REFER TO. I JUST HAD MY MEMORY. AND I HAD VERY KIND OF -- I MEAN, YOU TEND TO FORGET THINGS THAT DIDN'T WORK. I HAD JUST FORGOTTEN THE EXPERIMENTS IN SEPTEMBER AND THE ONES IN OCTOBER ON HUMAN DNA.

I REMEMBERED THAT FIRST EXPERIMENT, THE ONE THAT WE HAD ON THE TELEVISION THING HERE, REALLY . . . THAT WAS THE ONE THAT WORKED AND THAT WAS THE ONE I SAID, BOY, WOW.

AND IT DID WORK. THAT ONE WORKED THE FIRST TIME. BUT IT WASN'T THE FIRST EXPERIMENT.

I HAD TRIED OUT THOSE EXPERIMENTS IN HUMAN DNA BEFORE THAT. THIS WAS THE FIRST TIME I PICKED A REAL SIMPLE SYSTEM WHERE I COULD CONTROL EVERY SINGLE THING AND I KNEW WHAT IT WAS,

AND THEN THAT ONE WORKED.

AND THAT'S WHAT I'M -- I -- IF I HAD HAD MY NOTES AVAILABLE, I'D HAVE SAID, "WELL, I TRIED A FEW DUMB EXPERIMENTS BEFORE I DID THE REALLY GOOD ONE."

BUT . . . THAT'S WHAT I MEANT. I MEAN, IT WAS A MISTAKE IN THIS ARTICLE, BUT IT WASN'T A VERY SERIOUS MISTAKE.

Q. THERE'S ANOTHER SECTION IN THAT ARTICLE THAT I'D LIKE TO ASK YOU ABOUT IN WHICH YOU DESCRIBE A CONVERSATION YOU HAD WITH DR. LEDERBERG?

A. YES.

Q. AND YOU INDICATE HERE THAT YOU WERE TALKING TO DR. LEDERBERG IN THE SPRING OF 1984, AND THAT HE CAME OVER AND SAW YOUR POSTER AND ASKED IF IT WORKED. YOU SAID IT DID.

AND THEN YOU GO ON:

"AT ONE POINT, HE MENTIONED THAT ABOUT 20 YEARS PREVIOUSLY, AFTER DR. KORNBERG HAD DISCOVERED DNA POLYMERASE, THE TWO OF THEM HAD CONSIDERED THE NOTION THAT THE ENZYME COULD SOMEHOW BE HARNESSED TO MAKE LARGE QUANTITIES OF DNA. THEY HAD NOT FIGURED OUT EXACTLY HOW TO DO IT, HOWEVER."

YOU SAY: "I REMINDED HIM THAT OLIGONUCLEOTIDES WERE NOT READILY AVAILABLE AT THAT TIME AND THAT THERE WAS HARDLY ANY DNA SEQUENCE INFORMATION, EITHER."

NOW, WHEN DID THE NECESSARY OLIGONUCLEOTIDES AND NECESSARY SEQUENCE INFORMATION BECOME AVAILABLE?

A. WELL, NECESSARY FOR . . . FOR -- I MEAN, IT -- OLIGONUCLEOTIDES SLOWLY BECAME AVAILABLE LATE IN THE '60'S AND THEN MORE SO IN THE '70'S.

MR. FIGG: YOUR HONOR, THERE'S NO FOUNDATION FOR THIS QUESTION. DR. MULLIS TESTIFIED THAT HE NEVER WORKED WITH OLIGONUCLEOTIDES OR KNEW ANYTHING ABOUT THEM BEFORE 1980.

THE COURT: I ASSUME YOU CAN LAY A FOUNDATION FOR IT. I'M INCLINED TO JUST LET YOU GO AHEAD, BUT WHY DON'T YOU LAY A FOUNDATION?

Q. (BY MR. PASAHOW) DR. MULLIS, HAVE YOU REVIEWED THE LITERATURE ABOUT THE USE OF SEQUENCE INFORMATIONS IN MOLECULAR BIOLOGY?

A. WELL, YES. AS SOON AS I GOT INTERESTED IN -- AND STARTED DOING IT, I DID LOOK BACK OCCASIONALLY AT THE LITERATURE, AND SO I -- I WAS -- YOU KNOW, I WAS NOT PAINSTAKINGLY FAMILIAR WITH EVERY TURN OF EVENTS IN THE DEVELOPMENT OF THE SYNTHESIS OF OLIGONUCLEOTIDES, BUT I HAD PAPERS GOING BACK QUITE A WAYS, AND I -- I KNEW A GOOD BIT ABOUT WHEN OLIGONUCLEOTIDES HAD BECOME AVAILABLE, YES.

Q. AND DID YOU KNOW WHEN SEQUENCE INFORMATION BECAME AVAILABLE?

A. SEQUENCE INFORMATION BECAME REALLY WIDELY AVAILABLE AFTER SANGER, BUT, YEAH, I KNEW A LITTLE BIT OF THAT, TOO.

Q. CAN YOU EXPLAIN WHEN, IN YOUR OPINION, THE NECESSARY OLIGONUCLEOTIDES AND THE NECESSARY SEQUENCE INFORMATION TO DO PCR BECAME AVAILABLE.

A. CERTAINLY AFTER -- YOU KNOW, IN THE -- IN THE MIDDLE '70'S. '75, '76, '77. IF SOMEBODY HAD WANTED TO DO IT, THERE WAS NO PROBLEM -- THERE WOULD HAVE BEEN NO PROBLEM FINDING THE OLIGONUCLEOTIDES.

I -- I -- IT DEPENDED -- IT WOULD DEPEND A LOT ON WHERE YOU WERE, BUT I WOULD SAY IN A LAB THAT HAD OLIGONUCLEOTIDES IN IT, FOR INSTANCE LIKE IN KHORANA'S LAB, YOU COULD HAVE EASILY DONE IT BEFORE.

BUT I -- ANYBODY COULD HAVE -- ANYBODY THAT HAD ANY KIND OF REPUTATION AS A SCIENTIST COULD HAVE GOTTEN AN OLIGONUCLEOTIDE CHEMIST TO MAKE HIM A COUPLE OF OLIGONUCLEOTIDES IN 1975 TO 1977, AND THE SEQUENCE INFORMATION CAME POURING OUT AFTER THAT.

BUT THERE WAS ALREADY LOTS OF SEQUENCE INFORMATION BEFORE '77. IT'S JUST THAT IT WENT THROUGH AN ENORMOUS LEAP IN TERMS OF HOW FAST IT CAN BE GOTTEN IN '77, '78.

BY 1980, ANYBODY COULD HAVE DONE IT. I MEAN, YOU COULD BUY THEM. I THINK WE HAD TESTIMONY HERE YESTERDAY AND BEFORE THAT THEY BECAME REALLY READILY AVAILABLE, THAT YOU COULD JUST ORDER THEM FROM COMPANIES BACK IN THE '70'S AND EARLY '80'S.

Q. NOW, I'D LIKE TO ASK YOU TO EXPLAIN A COUPLE OF ITEMS FROM YOUR PATENT. I DON'T INTEND TO GO OVER ALL THE 30 OR SO COLUMNS.

BUT IF YOU'D TURN TO COLUMN 15, THERE'S A REFERENCE THERE TO EXAMPLE 1 IN COLUMN 15 AT LINE 45.

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MR. FIGG: IS THIS THE '202 PATENT?

MR. PASAHOW: YES. SORRY.

THE WITNESS: AND YOU WANT THE '195?

Q. (BY MR. PASAHOW) IN THE '202 PATENT.

A. IN THE '202. OKAY.

Q. THIS WOULD BE THE FIRST ITEM IN THE JURORS' NOTEBOOK.

A. COLUMN 15, RIGHT. EXAMPLE 1.

Q. WHAT IS EXAMPLE 1? ARE YOU FAMILIAR WITH THAT EXPERIMENT?

A. YEAH. EXAMPLE 1 IS -- AS WE'VE SAID, IT'S -- IT'S SORT OF HISTORICALLY THE FIRST PCR EXPERIMENT THAT WORKED. THAT'S -- IT'S THE ONE WHERE I MADE THE 25-BASE PAIR FRAGMENT FROM THE PBR PLASMID.

Q. EXAMPLE 2 IN THE NEXT COLUMN, COLUMN 16, ARE YOU FAMILIAR WITH THAT EXPERIMENT?

A. YES.

Q. AND WHAT -- WHAT DOES THAT EXPERIMENT INVOLVE?

A. WELL, THIS ONE HAS AN AWFUL LOT OF EXPERIMENTAL DETAIL IN IT, BECAUSE WE WANTED TO HAVE AT LEAST ONE EXAMPLE IN THERE THAT -- THAT GAVE THE EXPERIMENTAL DETAIL FOR EVERY TECHNIQUE THAT WE EMPLOYED.

SO THAT SORT OF -- IT TALKS ABOUT THE SYNTHESIS OF THE PRIMERS, LIKE HOW YOU COULD DO THE OLIGONUCLEOTIDE SYNTHESIS OF PRIMERS, WHERE YOU COULD GET DNA FROM. I MEAN, JUST -- IT GAVE OUT -- IT GAVE THE WHOLE -- THE WHOLE THING.

AND THEN IT TALKED ABOUT THE CONDITIONS OF THE

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POLYMERASE CHAIN REACTION, THAT -- WHERE WE WERE USING -- IN THIS CASE, WE WERE AMPLIFYING A -- SOME -- A SEQUENCE OUT OF HUMAN DNA, AND ALSO THIS SAME SEQUENCE THAT WE HAD OUT OF -- IN SOME PLASMIDS THAT CONTAINED IT SORT OF AS A MODEL.

AND THEN IT TALKS ABOUT, AFTER THE REACTION, HOW WE WENT ABOUT DETECTING IT AND PROVING THAT IT WAS, IN FACT -- THAT WHAT -- IT TELLS YOU HOW YOU COULD DETECT IT AND HOW YOU COULD PROVE THAT YOU HAD WHAT YOU HAD.

Q. NOW, THESE EXAMPLES GO ON A WAYS WITH A LOT OF DETAIL.

DO YOU THINK THAT SOMEONE WITH ORDINARY SKILLS IN A LABORATORY WOULD BE ABLE TO FOLLOW EXAMPLE 2 AND REPEAT THE WORK THAT'S DESCRIBED THERE?

A. THEY -- THEY CERTAINLY -- WITH ORDINARY SKILLS IN A LABORATORY, THEY COULD DEFINITELY DO THAT. THAT'S HOW -- WE WROTE IT FOR SOMEBODY THAT HAD ORDINARY SKILLS.

Q. AND THAT'S WHAT THIS DETAIL IS ABOUT?

A. YES.

Q. NOW, COULD YOU GO ON -- SKIPPING SEVERAL OF THESE EXAMPLES -- TO EXAMPLE 7 IN COLUMN 22.

A. OKAY.

Q. ARE YOU FAMILIAR WITH THE EXAMPLE THAT'S EXPLAINED IN WHAT IS -- I GUESS IT'S EXHIBIT 7A, SINCE THERE'S ALSO A 7B.

A. YES. THAT'S THE EXPERIMENT THAT WE HAD ON THE -- SOMEWHERE AROUND HERE, IS WHERE WE TOOK SAMPLES OUT AFTER EVERY CYCLE AND COUNTED THE AMOUNT OF COUNTS THAT HAD GONE INTO THE FRAGMENT

AFTER THAT NUMBER OF CYCLES AND PLOTTED IT AND MADE THAT LITTLE CURVE AND STUFF. THAT'S THE -- THAT'S WHAT THAT EXAMPLE IS TALKING ABOUT IS THAT SAME EXPERIMENT.

Q. SO THAT'S -- THAT'S THE EXAMPLE THAT LED TO THE GRAPH THAT WE LOOKED AT?

A. YES.

Q. DOES THAT EXAMPLE EXPLAIN HOW THE PCR REACTION WAS DONE SOMEWHERE?

A. YES. IT'S -- IN THE VERY FIRST PART OF IT, IT DESCRIBES THE REACTION CONDITIONS EXACTLY.

Q. COULD YOU EXPLAIN WHAT THOSE REACTION CONDITIONS WERE FOR US, JUST SO WE HAVE AN EXAMPLE OF THAT.

A. OKAY. WELL, I CAN READ IT FROM HERE:

"A TOTAL OF 100 FMOLES" --

THAT'S ANOTHER ONE OF THOSE WORDS LIKE PICOMOLES.

-- "OF PBR328 CONTAINING A 1.9 KILOBYTES INSERT FROM THE HUMAN BETA-GLOBIN A ALLELE, 50 NANOMOLES EACH ALPHA P32 DEOXYNTP AT 500 CURIES PER MOLE, AND ONE NANOMOLE OF EACH OF THE PRIMERS USED IN EXAMPLE 3" --

AND YOU CAN LOOK BACK AT EXAMPLE 3 AND FIND THE SEQUENCES OF THOSE PRIMERS. THIS IS -- THIS IS THE KIND OF -- THESE ARE THE KINDS OF -- THIS IS THE KIND OF DETAIL THAT YOU COULD USE TO DO THE EXPERIMENT ITSELF.

-- "WERE DISSOLVED IN A SOLUTION CONTAINING

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100 MICROLITERS OF 30 MILLIMOLAR OF TRIS-ACETATE" --

Q. WHAT'S THAT FOR?

A. THAT'S THE BUFFER. THAT'S TO KEEP THE PH AT -- AT THE -- LIKE A PH 7.9 IN THIS EXAMPLE IS WHERE WE SET -- THAT'S THE SORT OF CONTROL THE ACIDITY OR -- IN THE REACTION, JUST TO KEEP IT STEADY EVEN THOUGH SOME ACID-PRODUCING REACTIONS ARE TAKING PLACE.

-- "AT PH 7.9, 60 MILLIMOLAR SODIUM ACETATE" --

Q. WHAT'S THAT FOR?

A. IT'S A SALT. IT'S PART OF THE BUFFER THAT WE WERE UNDER THE IMPRESSION AT THAT TIME THAT THE . . . THE ENZYME MIGHT LIKE A LITTLE SALT. AND, IN FACT, IN BIOCHEMICAL REACTIONS, YOU USUALLY HAVE VARIOUS SALTS IN THERE. IN FACT, IT TURNS OUT IN THIS CASE IT WAS IMPORTANT.

-- "100 MILLIMOLAR DITHIOTHREITOL" --

THAT WAS TO KEEP THE ENZYMES STABLE. IT KEEPS THE ENZYME FROM OXYDIZING.

-- "AND TEN MILLIMOLAR MAGNESIUM ACETATE."

AND THAT'S IN THERE BECAUSE THE ENZYME LIKES TO INCORPORATE THE NUCLEOTIDES AS THEIR MAGNESIUM SALTS. IT WANTS THE MAGNESIUM TO BE ASSOCIATED WITH THEM AND IT ALSO LIKES TO HAVE THE MAGNESIUM ITSELF IN OTHER SPOTS.

"THIS SOLUTION WAS BROUGHT TO 100 DEGREES CENTIGRADE FOR TWO MINUTES AND COOLED TO 25 DEGREES

CENTIGRADE FOR ONE MINUTE. A TOTAL OF ONE MICROLITER CONTAINING 4.5 UNITS KLENOW FRAGMENT OF E. COLI DNA POLYMERASE 1 AND .09 UNITS OF INORGANIC PYROPHOSPHATASE" --

THAT WAS A NEW COMPONENT THAT -- THAT'S A COMPONENT WE PUT IN THIS REACTION AND IN SOME OTHERS, BUT WE DON'T PUT IT IN ALL OF THEM.

THE FUNCTION OF THAT WAS TO DESTROY A BYPRODUCT OF THE POLYMERIZATION REACTION, WHICH IS THE PART OF THE LITTLE SPRING I WAS TALKING ABOUT THAT POPS OFF OF THE NUCLEOTIDES. THOSE LITTLE SPRINGS I THOUGHT MIGHT ACCUMULATE. WE WANT TO GET RID OF THEM. THEY'RE CALLED PYROPHOSPHATES. I PUT THAT IN THERE.

-- ".09 UNITS INORGANIC PYROPHOSPHATASE WAS ADDED TO PREVENT THE POSSIBLE BUILD-UP OF PYROPHOSPHATE IN THE REACTION MIXTURE, AND THE REACTION WAS ALLOWED TO PROCEED FOR TWO MINUTES AT 25" --

ARE WE GOING TO BORE EVERYBODY WITH THIS?

Q. WELL, LET'S SEE IF WE CAN JUST GET TO THE END OF THE CYCLE HERE.

A. OKAY.

-- "WAS ALLOWED TO PROCESS FOR TWO MINUTES AT 25 DEGREES CENTIGRADE, AFTER WHICH THE CYCLE OF HEATING, COOLING, ADDING ENZYME, AND REACTING WAS REPEATED NINE TIMES."

Q. NOW, STOPPING THERE, THAT'S THE END OF THE PCR PART OF THE EXAMPLE; IS THAT RIGHT?

A. YES. THAT'S THE PART -- THE REACTION PART.

Q. SO THAT WOULD BE A PROTOCOL FOR DOING THE REACTION THAT YOU DID IN THIS EXPERIMENT?

A. YES.

Q. AND THEN ONE MORE EXPERIMENT I'D JUST LIKE TO HAVE YOU IDENTIFY FOR US, AND THAT'S THE EXPERIMENT THAT'S EXAMPLE TEN IN COLUMN 25.

ARE YOU FAMILIAR WITH THAT ONE?

A. YES.

Q. WHAT IS THAT EXAMPLE?

A. THAT'S THE EXAMPLE OF THE USE OF THE NESTED PRIMERS TO DETECT THE SINGLE-COPIED HUMAN GENE WITHOUT USE OF RADIOACTIVE MATERIAL AT ALL, THE ONE THAT I DESCRIBED THERE WHERE I CAN SEE IT.

Q. WITH THE NESTED PRIMERS?

A. YES, THE NESTED PRIMER.

Q. AND DO YOU HAVE THE RESULTS OF THAT SHOWN IN THE PATENT SOMEWHERE?

A. I BELIEVE IT'S ONE OF THE -- IT'S PROBABLY THE FINAL FIGURE. IT WAS KIND OF THE -- YEAH. IT'S THE ICING ON THE CAKE THERE, JUST LIKE -- IT'S RIGHT HERE.

Q. LET ME BORROW THIS ONE WHICH IS CLEAR.

AND COULD I ASK YOU TO POINT OUT WHAT THESE DIFFERENT

BANDS MEAN.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) IF YOU COULD JUST SHORTCUT IT AND SHOW US WHAT THE PRINCIPAL ITEMS ARE ON IT.

A. OKAY. I THINK I'VE ACTUALLY MEMORIZED THE GEL, BECAUSE I'VE PRESENTED IT -- A LOT OF THESE.

IT SHOWS . . . OKAY. IT SHOWS THIS 58-BASE PAIR FRAGMENT THAT I DESCRIBED ON THAT POSTER SOME WHILE AGO.

THIS IS COMPLICATED LOGISTICS HERE.

THE 58-BASE PAIR FRAGMENT IS THE FINAL PRODUCT OF THIS REACTION. IT STARTS OUT MAKING 110 MER, WHICH YOU CAN SEE A LITTLE UP HERE.

BUT WHAT WE HAVE HERE IS A SET OF MARKERS, UP HERE, INCLUDING A SYNTHETIC 58 MER I PUT THERE TO KNOW EXACTLY WHAT I WAS DOING.

OKAY. AND THEN THIS IS A LANE WHERE I'VE TAKEN THE DNA AND AMPLIFIED IT THROUGH TWO SETS OF PCR REACTIONS, USING THE NESTED PRIMERS, AND I'VE PRODUCED THIS 58-BASE PAIR PRODUCT.

IN THIS LANE, I'VE -- THAT'S A CONTROL LANE THAT I PUT IN THERE. WHAT I DID WAS, I CUT THE DNA THAT I WAS GOING TO START WITH, THE TARGET DNA, WITH AN ENZYME THAT WOULD CUT RIGHT IN THE MIDDLE OF THE FRAGMENT THAT I WAS GOING TO TRY TO AMPLIFY, SO WHEN I TRIED TO AMPLIFY IT, THAT FRAGMENT WOULDN'T BE THERE. SO I SHOULD GET NOTHING.

AND BY -- AND WHEN I GET NOTHING -- YOU GET NOTHING IN

AN EXPERIMENT LIKE THAT, THAT'S A CONTROL. IT SAYS THIS REALLY DID RESULT FROM AMPLIFICATION OF THAT SEQUENCE BECAUSE, WHEN I SPECIFICALLY CUT THAT SEQUENCE OUT AND THEN STARTED THE REACTION, I DIDN'T GET THAT FRAGMENT.

NOW, THIS IS A REACTION WHICH HAD -- THIS IS ANOTHER CONTROL, WHERE I -- THIS IS THE -- USING -- STARTING WITH SICKLE CELL DNA, WHERE, WHEN I CUT IN THE MIDDLE OF THAT, IT DOESN'T HAVE THE RESTRICTION SITE, SO I CAN CUT IT AND AMPLIFY IT AND I'LL STILL GET A FRAGMENT.

OKAY. SO THAT'S TELLING YOU, HEY, THIS IS WORKING PRETTY GOOD. IT'S VERY SPECIFIC.

IN THIS ONE, I TOOK SOME WHALE DNA -- DNA FROM THE WHALE -- OURS WAS SALMON SPERM DNA, I THINK THAT WAS.

THIS WAS SALMON SPERM DNA, AND IT SHOULD NOT HAVE A BETA-GLOBIN SEQUENCE IN IT; OKAY? SO IT DIDN'T. IT SHOWED NOTHING.

YOU CAN SEE THAT THAT'S THE -- THIS IS THE KIND OF STUFF THAT SOMETIMES ENDS UP ON TOP OF THE GEL WHICH YOU WOULD HAVE THOUGHT OF AS BEING THE PRODUCT IF YOU DIDN'T HAVE A GEL. SO THAT'S UP THERE AND NOT DOWN HERE.

THIS IS A COUPLE -- THIS IS A LANE HERE WHERE I TOOK THIS PRODUCT AND CUT IT WITH AN ENZYME, THE SAME ONE THAT I HAD CUT WITH BEFORE AMPLIFICATION AND GOTTEN THIS.

IF I -- AFTER AMPLIFICATION, IF I CUT THIS FRAGMENT WITH THAT SAME ENZYME, I GET THESE TWO LITTLE PIECES WHICH ARE

27 AND 31 BASE PAIRS LONG, WHICH IS WHAT I SHOULD HAVE GOTTEN. THAT TOLD ME THIS WAS THE RIGHT PIECE.

IT CAME BECAUSE IT WAS A VERY SPECIFIC AMPLIFICATION. IT PRODUCED SOMETHING, EXACTLY WHAT IT SHOWED, AND IT WAS A PRETTY NICE DEMONSTRATION THAT I HAD SUCCESSFULLY AMPLIFIED A HUMAN -- A SINGLE-COPIED HUMAN SEQUENCE WHERE I COULD SEE IT.

THAT'S MY FAVORITE GEL.

(WITNESS RESUMES WITNESS STAND.)

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) HAVE YOU GENERALLY FOLLOWED THE LITERATURE WHERE PEOPLE HAVE PUBLISHED ARTICLES IN WHICH THEY DESCRIBED USING THE PCR PROCESS?

A. AT FIRST, I FOLLOWED IT VERY TIGHTLY. IT -- IT'S LIKE -- IT'S GOTTEN TO THE POINT WHERE YOU CAN'T REALLY FOLLOW IT SPECIFICALLY ANY MORE, BECAUSE THERE'S TOO MANY PAPERS.

THERE'S -- I DO HAVE A -- I SUBSCRIBE TO A -- AN INDEXING OR A KIND OF REFERENCING KIND OF SERVICE THAT THEY SEND ME A LIST OF ALL THE PAPERS THAT HAVE QUOTED PCR EVERY -- I GET IT EVERY WEEK OR SO, AND SO I HAVE A BIG COLLECTION.

I MEAN, THERE ARE BIBLIOGRAPHIES, KIND OF, THAT HAVE BEEN PREPARED BY CETUS -- PERKIN-ELMER/CETUS THAT -- THE COMPANY THAT OWNS THIS PATENT -- AND THEY -- THOSE ARE DESCRIBED -- I MEAN, THEY DESCRIBE THE ACCUMULATION OF REFERENCES TO PCR.

Q. ARE YOU FAMILIAR, FOR EXAMPLE, WITH EXHIBIT B-221?

A. YEAH. THIS IS THE BOOK I'M TALKING ABOUT. THIS IS A --

JUST A BUNCH OF ENTRIES SHOWING THAT -- EVERY SINGLE -- MOST OF THE PAPERS, AT LEAST, THAT HAVE QUOTED PCR IN THE LAST WHATEVER, SINCE IT STARTED GETTING QUOTED IN 1985.

Q. NOW, JUST FOR A POINT OF REFERENCE, WE GRAPHED THE NUMBER OF ARTICLES FROM EACH YEAR OF THAT BOOK, AND IT PRODUCES A GRAPH WHICH LOOKS LIKE THIS.

AND YOU SEE THAT, STARTING IN 1985, THERE ARE -- THERE ARE, OF COURSE, THE FEW ARTICLES THAT WERE GENERATED BY THE CETUS SCIENTISTS. BUT EVEN IN 1986, THERE AREN'T VERY MANY. IN 1987, IT'S GETTING UP SLOWLY.

DO YOU HAVE A VIEW AS TO WHY THE INCREASE IN ARTICLES DESCRIBING THE USE OF PCR GREW IN THE MANNER IT DID?

MR. FIGG: THAT CALLS FOR SPECULATION, YOUR HONOR.

THE COURT: THE OBJECTION IS OVERRULED. I'LL ALLOW YOU TO GO INTO IT IN CROSS-EXAMINATION.

THE JURY WILL GIVE IT THE WEIGHT THEY THINK IT'S ENTITLED TO BASED UPON HIS ANSWER AND THE CROSS-EXAM.

THE WITNESS: I -- WELL, THE FIRST THREE THAT ARE IN 1985 IS PRETTY EASY TO EXPLAIN. THAT WAS OUR PAPERS.

AND THEN IN 1986, A LOT OF PEOPLE BY THEN HAD STARTED TO -- HAD HEARD ABOUT IT. AT COLD SPRING HARBOR, EVERYBODY FOUND OUT ABOUT IT.

IT TAKES PEOPLE A LITTLE WHILE TO START CHANGING ROUTINES IN THEIR LAB, ADOPTING A NEW ROUTINE OR SOMETHING. IT'S -- THERE'S A CERTAIN TURNAROUND TIME.

AND SO I WAS -- I WAS ACTUALLY QUITE HEARTENED BY THE FACT THAT, IN -- BY THE END OF '86, THERE WERE 20; AND THEN '87, THERE WERE 75. THAT WAS ABOUT -- I THOUGHT NOW IT WAS GETTING -- BY THE TIME IT WAS 75, I WAS STARTING TO NOT KNOW EVERYBODY THAT WAS DOING THEM.

AND I THINK THAT THAT'S . . . I MEAN, I DON'T SEE QUITE WHAT THE QUESTION IS.

WHY WOULDN'T IT BE LIKE THAT? IT SEEMS . . . IT HAS THAT -- I MEAN, THAT'S -- I THINK THAT'S A NORMAL RESPONSE TIME OF THE SCIENTIFIC COMMUNITY TO SOME DEVELOPMENT.

Q. (BY MR. PASAHOW) NOW, YOU'RE AWARE THAT PCR WAS SELECTED BY SCIENCE MAGAZINE IN ITS DECEMBER 1989 ISSUE AS THE MOLECULE OF THE YEAR, OR THE DISCOVERY OF THE YEAR.

A. YES. WHEN MY ISSUE OF SCIENCE CAME IN MY MAILBOX, I SAW THAT ON THERE, AND I WAS . . . I WAS A LITTLE SURPRISED, BUT I WAS VERY HAPPY ABOUT IT.

Q. DO YOU HAVE A VIEW AS TO THE IMPORTANCE OF PCR ON THE SCIENTIFIC COMMUNITY?

A. IT HAS TRANSFORMED COMPLETELY A LOT OF AREAS OF SCIENCE, AND I'D SAY LIKE, AS AN EXAMPLE, IN HUMAN GENETICS, THE PEOPLE THAT GAVE ME THAT ALLEN AWARD THIS YEAR.

AT THAT MEETING IN CINCINNATI, THERE WERE ABOUT 6,000 PEOPLE THERE AND THE -- AND IN THE AUDITORIUM, THEY HAD A GREAT BIG SORT OF EXHIBITION HALL WHERE EVERYBODY BROUGHT POSTERS OF THEIR WORK. AND THERE WERE PROBABLY ABOUT A THOUSAND POSTERS

THERE, MAYBE A LITTLE MORE. AND I'M -- THERE WERE AT LEAST 800 OUT OF THAT THOUSAND PAPERS THAT PRESENTED THERE THAT INVOLVED PCR.

AND WALKING AROUND IN THAT AUDITORIUM, LOOKING AT ALL THIS STUFF ON PCR, IT TRANSFORMED A LOT OF PEOPLE'S RESEARCH CAREERS, AND IT CERTAINLY TRANSFORMED MINE.

AND I THINK IT'S -- IT'S HAD A BIG IMPACT. I MEAN, THERE'S MAGAZINE ARTICLES ABOUT IT ALL THE TIME, AND THERE'S VARIOUS USES OF IT THAT, YOU KNOW, PEOPLE KEEP DISCOVERING.

Q. WHAT DO YOU THINK ARE THE MOST SIGNIFICANT USES OF PCR NOW?

A. THE MOST SIGNIFICANT ONES?

WELL, IT'S HAVING A REALLY BIG IMPACT ON -- ON THE EFFORT TO SEQUENCE THE HUMAN GENOME. I -- THOSE -- I THINK THAT IT'S A VERY SIGNIFICANT KIND OF PROCESS THAT IS GOING TO BE REALLY GLOBALLY . . . IT WILL HAVE A BIG EFFECT GLOBALLY.

TO HAVE THE SEQUENCING OF THE HUMAN GENOME WILL -- IT REALLY WILL CHANGE MEDICAL SCIENCE. AND NOT JUST HUMAN GENOMES BUT OTHER GENOMES, PARTICULARLY IN TERMS OF ITS IMPACT ON HUMANS.

I THINK THE KNOWLEDGE OF THE HUMAN GENOME AND THE ABILITY TO READ THAT, TO READ THAT INFORMATION WHICH PCR ALLOWS, THAT'S -- THE PCR HAS -- HAS -- HAS REALLY ALLOWED PEOPLE TO READ THE GENETIC INFORMATION THAT'S BEEN ACCUMULATING IN OUR -- IN OUR CELLS FOR, YOU KNOW, BILLIONS OF YEARS.

THIS IS THE FIRST CENTURY IN WHICH PEOPLE CAN REALLY

LOOK BACK AND SEE WHAT MAKES THEM TICK, AND IT'S -- I THINK THAT'S PRETTY SIGNIFICANT.

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

THE COURT: IS THIS A GOOD POINT TO TAKE A BREAK, I THINK --

MR. FIGG: I THINK SO.

THE COURT: -- AND THEN COMMENCE WITH CROSS-EXAMINATION?

YOU MAY STEP DOWN.

LADIES AND GENTLEMEN, WE'LL RECESS FOR ABOUT 10, 15 MINUTES.

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

(JURY EXCUSED)

(RECESS TAKEN AT 11:27 A.M.)

(CONTINUED ON NEXT PAGE, NOTHING OMITTED)

MR. PASAHOW: YOUR HONOR, BEFORE MR. FIGG STARTS, MS. MORIYAMA POINTS OUT I OMITTED TO ASK HER TO MARK THE LAST PAGE OF NOTES THAT DR. MULLIS WROTE ON THE CHART HERE, THIS IS HIS PRIMER EXPLANATION.

THE COURT: THAT'S ONLY ONE THAT REMAINS UNMARKED?

MR. PASAHOW: YES.

THE CLERK: DEFENDANTS B-254 MARKED FOR IDENTIFICATION ONLY.

(DEFENDANT'S EXHIBIT B-254 MARKED FOR IDENTIFICATION)

THE COURT: YES.

MR. FIGG: THANK YOU, YOUR HONOR.

CROSS-EXAMINATION

BY MR. FIGG:

Q. STILL A LITTLE BIT OF MORNING LEFT, DR. MULLIS. GOOD MORNING.

A. GOOD MORNING, MR. FIGG.

Q. DOCTOR, I'D LIKE TO BEGIN BY GOING INTO SOME OF YOUR GENERAL BACKGROUND IN A LITTLE MORE DETAIL THAN MR. PASAHOW DID.

I THINK IT CAME OUT THAT YOU'RE NO LONGER AN EMPLOYEE OF CETUS CORPORATION, ARE YOU?

A. NOT -- NOT DIRECTLY.

Q. YOU'RE NOT AN EMPLOYEE, ARE YOU?

A. I'M NOT AN EMPLOYEE OF CETUS AT ALL.

Q. AND YOU QUIT YOUR JOB AT CETUS IN 1986?

A. YES.

Q. YOU'RE NOW A CONSULTANT TO CETUS, DID I HEAR YOU CORRECTLY?

A. I'M A CONSULTANT ACTUALLY TO MC CUTCHEN, DOYLE, BROWN & ENERSEN, THE PEOPLE THAT ARE DOING THE CASE. CETUS IS PAYING ME THROUGH THEM.

Q. YOU'RE -- I'M SORRY.

A. SOMETHING LIKE THAT -- THEIR ARRANGEMENT IS, I THINK, THAT CETUS IS PAYING ME THROUGH THEM. I'M EMPLOYED BY MC CUTCHEN, DOYLE.

Q. YOU'RE A CONSULTANT TO CETUS' LAWYERS?

A. YES.

Q. AND PRIOR TO THAT TIME AFTER YOU QUIT YOUR JOB AT CETUS, DID YOU DO ANY CONSULTING WORK FOR CETUS?

A. NO CONSULTING WORK DIRECTLY FOR CETUS, THAT I CAN REMEMBER.

Q. AND DIRECTLY FOR CETUS?

A. I WAS TRYING TO THINK -- I THINK I NEVER DID ANY CONSULTING WORK FOR THEM.

Q. YOU BASICALLY HAVE NO CONTACT WITH CETUS AFTER YOU LEFT IN '86 UNTIL YOU STARTED CONSULTING WITH CETUS' LAWYERS?

A. ONLY SOCIALLY WITH PEOPLE AT CETUS.

Q. AND YOU BECAME A CONSULTANT TO CETUS' LAWYERS RIGHT AFTER THIS LAWSUIT BEGAN?

A. YES.

Q. AM I CORRECT THAT THE ONLY AREAS OF YOUR CONSULTATION WITH CETUS OR CETUS' LAWYERS RECENTLY HAS BEEN IN CONNECTION WITH

THIS LAWSUIT?

A. YES.

Q. AND YOU'RE BEING COMPENSATED BY THEM AT A RATE OF $2,000 PER DAY FOR THAT CONSULTATION?

A. YES, I AM.

Q. YOU'VE BEEN IN THE COURTROOM HERE SINCE THE TRIAL BEGAN, I BELIEVE?

A. YES, I HAVE.

Q. AND YOU PUT IN A NUMBER OF DAYS PRIOR TO THE BEGINNING OF THE TRIAL I SUSPECT?

A. YES.

Q. HOW MANY?

A. I HAVEN'T COUNTED THEM UP. THEY AMOUNT UP TO A FAIRLY SUM OF DAYS, THOUGH.

Q. WELL, CAN YOU GIVE US AN IDEA, WAS IT TEN, OR 20, OR 30?

A. PROBABLY IS GOING TO COME DOWN TO 30, SOMETHING LIKE THAT, 30 OR 40 DAYS.

Q. THAT WAS BEFORE THE LAWSUIT BEGAN?

A. ACTUALLY -- I REALLY DON'T KNOW. I HAVEN'T FIGURED OUT EXACTLY. IT'S BEEN SOME NUMBER OF DAYS, PROBABLY 30 OR 40 BEFORE. COULD BE -- IT MAY BE 20 OR 30.

Q. WHEN YOU BEGAN YOUR TESTIMONY YESTERDAY YOU INDICATED TO MR. PASAHOW THAT THE '202 AND THE '195 PATENTS WHICH YOU'VE TALKED ABOUT DURING YOUR TESTIMONY WERE YOUR PATENTS. DO YOU RECALL SAYING THAT?

A. I DID SAY THAT. IT WAS A LITTLE BIT BROADER, SHOULD HAVE BEEN THE '202 IS MY PATENT. IT'S NOT THAT I OWN IT, BUT I WROTE IT. CETUS OWNS IT. '195 HAS OTHER INVENTORS ON IT BESIDE ME.

Q. NEITHER OF THE PATENTS ARE REALLY YOUR PATENT, THEY BELONG TO CETUS CORPORATION?

A. THEY'RE THE PROPERTY OF CETUS CORPORATION, YES.

Q. YOU HAVE NO LICENSE OR RIGHT TO PRACTICE UNDER THOSE PATENTS?

A. WELL, I ACTUALLY MAY END UP HAVING THE LICENSE IF I WANT ONE. OTHER PEOPLE -- ANYBODY WHO WANTS TO USE THOSE PATENTS, IF IT'S ALL RIGHT WITH CETUS, CAN PAY THEM MONEY AND USE THEM. I DON'T HAVE -- THE PATENTS DO NOT BELONG TO ME, I THINK THAT'S ESTABLISHED.

Q. WELL, YOU SAID ANYONE WHO WANTS TO PAY CETUS MONEY CAN HAVE THE RIGHT TO USE THEM. DO YOU HAPPEN TO KNOW WHETHER CETUS HAS GRANTED EXCLUSIVE RIGHTS IN IN CERTAIN FIELDS SUCH THAT THEY COULD NOT GRANT RIGHTS TO ANYONE ELSE SUCH AS YOURSELF?

A. WELL, IN CERTAIN AREAS I BELIEVE THEY DO HAVE SOME -- SOME -- I'M NOT REALLY CERTAIN ABOUT THAT, MR. FIGG. I KNOW THERE IS AN ARRANGEMENT WITH HOFFMAN-LA ROCHE THAT IS AT LEAST NOMINALLY EXCLUSIVE, BUT I KNOW OF OTHER COMPANIES THAT HAVE LICENSES WITH CETUS TO DO IN VITRO DIAGNOSIS. I'M CONSULTING FOR ONE OF THEM IN SANTA MONICA.

IT'S NOT THAT NOBODY CAN USE -- PLENTY OF -- I'M NOT REALLY SURE WHAT YOUR QUESTION IS. I DON'T UNDERSTAND THE LEGAL

DOCUMENTS INVOLVED BETWEEN CETUS AND HOFFMAN-LA ROCHE.

Q. YOU DON'T KNOW WHAT THAT ARRANGEMENT IS?

A. NO, I'M NOT PRIVY TO ANYTHING.

Q. NOW, I BELIEVE YOU TESTIFIED YESTERDAY THAT WHEN YOU BEGAN WITH CETUS YOU WERE WORKING IN THE OLIGONUCLEOTIDE SYNTHESIS LABORATORY?

A. YES.

Q. AND YOUR PRIMARILY DUTY THERE WAS TO SYNTHESIZE THESE LITTLE SHORT PIECES OF DNA THAT WE CALL OLIGONUCLEOTIDES?

A. YES.

Q. AS I RECALL THAT WAS ABOUT 90 PERCENT OF YOUR RESPONSIBILITY UP TO 1983?

A. AS YOU RECALL?

Q. IS THAT CORRECT?

A. WELL, EVERYBODY AT CETUS HAD -- YOU MUST BE REFERRING TO THE FACT THERE WAS A POLICY THAT 10 PERCENT OF YOUR TIME, IF YOU WERE A SCIENTIST, COULD BE PUT ON PROJECTS THAT YOU WANTED TO WORK ON. IS THAT WHAT YOU MEAN?

Q. NO. I'M ASKING YOU, IS IT TRUE THAT ABOUT 90 PERCENT OF YOUR RESPONSIBILITIES IN THE LABORATORY UP TO 1983 WERE TO SYNTHESIZE OLIGONUCLEOTIDES?

A. YES.

Q. DO YOU RECALL THE SIZE OF THE OLIGONUCLEOTIDES THAT YOU WERE MAKING AT CETUS DURING THAT TIME FRAME?

A. UP TO 1983?

Q. UH-HUH.
A. YES.
Q. HOW MANY OTHER PEOPLE WERE WORKING IN THE OLIGONUCLEOTIDE SYNTHESIS LABORATORY?
A. THERE WERE FOUR OTHER PEOPLE FROM -- MAYBE A FIFTH ONCE IN AWHILE.
Q. THAT WAS IN THE 1983 TIME FRAME?
A. IN '83, YES.
Q. HOW LONG WERE THESE OLIGONUCLEOTIDES YOU WERE SYNTHESIZING, LET'S SAY, IN EARLY 1983, GENERALLY?
A. EARLY '83 WE PROBABLY GOTTEN UP TO 40 LONG SOMETIMES. THEY WERE GENERALLY IN THE RANGE OF 20, 20, 25, 30.
Q. MOST OF THEM WERE IN THE RANGE OF 20, 25 TO 30?
A. THAT'S MY RECOLLECTION.
Q. AS I UNDERSTAND THE OLIGONUCLEOTIDE LABORATORY WAS PROVIDING OLIGONUCLEOTIDES AS A SERVICE TO THE OTHER SCIENTISTS WHO WERE WORKING AT CETUS?
A. YES.
Q. THESE OTHER SCIENTISTS AT CETUS WERE USING THESE OLIGONUCLEOTIDES AS PRIMERS AND AS PROBES, ISN'T THAT CORRECT?
A. YES.
Q. AND WHEN WHEN WE SAY THEY WERE USING THEM AS PROBES, THEY WERE, IN THAT CASE THEY WERE RADIOACTIVELY LABELED OLIGONUCLEOTIDES AND THE SCIENTISTS WERE USING THEM TO DETECT DNA IN A MIXTURE OF DNA?

A. THAT'S ROUGHLY CORRECT.

Q. THAT'S WHAT THEY WERE USING THEM FOR, TO THE BEST OF YOUR KNOWLEDGE?

A. THEY WERE USING THEM -- WHEN THEY WERE USING THEM FOR PROBES, THEY WERE LABELING THEM USUALLY AND THEY WERE TRYING TO DETECT SEQUENCES OF DNA IN ALL KIND OF DIFFERENT CONTEXTS.

Q. THAT WAS THE -- THAT USE OF THESE AS PROBES IS THE TECHNIQUE CALLED HYBRIDIZATION PROBING SOMETIMES?

A. YES. THAT'S THE PROCESS THAT'S EMPLOYED AS THAT SORT OF THE CENTER OF THE PROBING PROCESS.

Q. THAT WAS THE PROCESS THAT'S DEFINED BY THE LAST TWO STEPS IN CLAIM 1 OF THE '195, RIGHT, DO YOU RECALL THAT?

A. IN THE '195 THE LAST TWO STEPS?

Q. YES.

A. THAT HAS TO DO WITH DETECTING THE AMPLIFIED PRODUCT, THE RADIOACTIVE PROBE?

Q. RIGHT.

A. YES.

Q. HOW MANY OLIGONUCLEOTIDES WERE YOU AND YOUR LAB MAKING IN 1983 FOR THIS PURPOSE? WAS IT TEN, WAS IT 50, A HUNDRED?

A. MORE LIKE 50 TO A HUNDRED. MAYBE -- THE YEAR I'M NOT QUITE SO CLEAR ON, BUT I'D SAY ABOUT '83, IN THAT YEAR, PROBABLY MADE A HUNDRED, MAYBE MORE.

Q. SO THE USE OF THESE LABELED OLIGONUCLEOTIDES FOR HYBRIDIZATION PROBE DETECTION WAS FAIRLY WIDESPREAD AT CETUS IN

1983?

A. YES.

Q. SCIENTISTS AT CETUS WERE ALSO USING SOME OF THESE FOR PRIMER EXTENSION REACTIONS IN 1983; IS THAT CORRECT?

A. YES.

Q. AND, AGAIN, THEY WOULD BE DOING THAT TO MAKE PROBES IN SOME -- EXCUSE ME, IN THEIR CLONING WORK?

A. THERE WERE MANY DIFFERENT CONTEXTS IN WHICH PRIMER EXTENSION WAS DONE.

Q. BUT ONE OF THEM WAS TO USE PRIMER EXTENSION TO MAKE A COPY OF DNA THAT WOULD THEN BE CLONED; IS THAT CORRECT?

A. YES. A COPY OF -- CDNA CLONING INVOLVED MAKING A COPY OF RNA AND ANOTHER COPY OF CDNA.

Q. WOULD YOU START OUT WITH A PIECE OF RNA AND THEN WOULD YOU TAKE ONE OF THE PRIMERS THAT YOUR LAB MADE, STICK IT ON THAT RNA AND USE A DNA POLYMERASE TO EXTEND IT OUT AND MAKE A COMPLEMENTARY COPY IN THE FORM OF DNA; IS THAT CORRECT?

A. YES.

Q. AND THAT WAS WIDELY USED PROCEDURE AT CETUS IN 1983?

A. UH-HUH. THAT WAS FAIRLY WIDELY USED ALL OVER BY 1983. IT WAS ONLY ONE DNA POLYMERASE THAT WOULD DO THAT, IT'S CALLED REVERSE TRANSCRIPTASE.

Q. WHEN YOU SAY IT WAS WIDELY KNOWN ALL OVER, YOU MEAN NOT ONLY AT CETUS, IN MOLECULAR BIOLOGY LABS ALL OVER THE WORLD?

A. YES, THAT'S WHAT I MEAN BY ALL OVER.

Q. NOW, DOCTOR, WHEN YOU JOINED CETUS CORPORATION YOU HAD NOT DONE ANY GENE CLONING WORK UP TO THAT POINT, HAD YOU?

A. NO, NOT AT ALL.

Q. SO YOU HAD NEVER USED YOURSELF THE PRIMER EXTENSION REACTION IN ANY SORT OF CLONING EXPERIMENTS?

A. NO, I HAD NOT.

Q. AND YOU HAD NEVER DONE AN ELECTROPHORETIC SEPARATION OF DNA AT THE TIME YOU JOINED CETUS CORPORATION, HAD YOU?

A. I DON'T RECALL EVER DOING THAT. I MAY HAVE HAD TO DO SOME KIND OF ELECTROPHORESIS OF DNA AS A GRADUATE STUDENT, BUT NOT THE KIND I WAS LATER TO BE DOING AT CETUS.

Q. WELL, DO YOU RECALL AT YOUR DEPOSITION WHEN I ASKED YOU:

HAD YOU EVER DONE ELECTROPHORETIC SEPARATION OF DNA PRIOR TO JOINING CETUS?

AND YOU RESPONDED:

"I HAD NOT -- I HAD DONE -- I HAD NOT DONE DNA, I HAD NOT DONE ELECTROPHORETIC SEPARATIONS OF DNA."

A. I DON'T RECALL IT, BUT IT SOUNDS LIKE THAT'S ME TALKING THERE. SORT OF THE SAME THING I SAID THIS TIME, I DON'T RECALL. I ADDED TO THAT I MAY HAVE DONE IT AS A GRADUATE STUDENT IN SOME OTHER CONTEXT.

THERE WERE COURSES THAT I HAD TO TAKE, THERE WERE LABORATORY COURSES AND MAYBE ONE EXPERIMENT I DID THAT HAD TO DO WITH ELECTROPHORESIS OF DNA.

Q. YOU RECALL SOMETHING NOW YOU DIDN'T RECALL WHEN I ASKED YOU

THAT QUESTION AT YOUR DEPOSITION?

A. NO, MR. FIGG, I DIDN'T RECALL IT. I JUST SPOKE A LITTLE BIT DIFFERENTLY AND SUGGESTED THAT PERHAPS I MIGHT HAVE DONE AN EXPERIMENT OR TWO TO THE CONTEXT OF BEING A GRADUATE STUDENT IN THE 1970'S AT BERKLEY.

IF YOU CONSIDER THAT CHANGING MY TESTIMONY I THINK YOU'RE PICKING AT HAIRS.

Q. I DIDN'T ACCUSE YOU OF CHANGING YOUR TESTIMONY, DR. MULLIS. I ASKED YOU IF YOU REMEMBER SOMETHING NOW THAT YOU HAD NOT REMEMBERED WHEN I ASKED YOU THAT QUESTION AT YOUR DEPOSITION?

A. I WOULD NOT AGREE WITH YOU. I DIDN'T REMEMBER SOMETHING DIFFERENT, I JUST ADDED THE PROVISO THERE THAT I MIGHT HAVE FORGOTTEN SOMETHING COMING FROM MY GRADUATE STUDENT DAYS I DIDN'T HAPPEN TO SAY THAT DURING THE DEPOSITION. I DON'T UNDERSTAND WHAT YOU'RE TALKING ABOUT.

Q. IN ANY EVENT, LET'S PUT IT THIS WAY: YOU WOULD NOT HAVE CONSIDERED YOURSELF EXTENSIVELY SKILLED IN THE ELECTROPHORETIC SEPARATION TECHNIQUE INVOLVING DNA IN 1980 WHEN YOU JOINED CETUS, IS THAT A FAIR STATEMENT?

A. I WOULD NOT HAVE CONSIDERED MYSELF AN EXPERT OF THE EFFECT AT THAT POINT, NO.

Q. YOU HAD NEVER DONE A SEQUENCING REACTION AT THE TIME YOU STARTED WORKING AT CETUS WITH YOUR OWN HANDS?

A. I NEVER HAD DONE ONE WITH MY OWN HANDS, NO.

Q. AND SEQUENCING IS ONE OF THESE OTHER REACTIONS THAT INVOLVES

THE PRIMER EXTENSION REACTION?

A. IT DEFINITELY IS BASED ON THE PRIMER EXTENSION. WE USED THE SANGER TECHNIQUE.

Q. NOW, YOU DREW A PICTURE FOR MR. PASAHOW INDICATING YOU HAD DONE SOME EXPERIMENTS LOOKING AT OLIGONUCLEOTIDES IN A SPECTROPHOTOMETER AND DETERMINING THE TEMPERATURES AT WHICH THEY WOULD ANNEAL AND COME BACK APART. DO YOU RECALL THAT TESTIMONY?

A. YES.

Q. YOU WEREN'T SUGGESTING THAT YOU WERE THE FIRST SCIENTIST EVER TO STUDY THAT PHENOMENA, ARE YOU?

A. I WASN'T EVEN SUGGESTING I WAS STUDYING IT. I SAID I WAS PLAYING AROUND WITH OLIGONUCLEOTIDES AND I DEFINITELY DID NOT DISCOVER THAT OLIGONUCLEOTIDES HYBRIDIZE AT LOW TEMPERATURE AND MELT AT HIGH THE TEMPERATURE.

Q. THAT WORK WAS DESCRIBE IN THE LITERATURE MUCH EARLIER?

A. THOSE EXPERIMENT WERE NOT THE ONES THAT I DID. THE IDEA WAS CERTAINLY THERE AND OTHER EXPERIMENTS THAT GOT AT THAT INFORMATION WERE, THE EXACT WAY I DID IT. I DON'T THINK I'VE EVER SEEN ANYBODY DO IT THAT WAY.

Q. YOU'RE FAMILIAR WITH A TECHNIQUE CALLED SOUTHERN BLOTTING, I BELIEVE?

A. YES, I AM.

Q. AND SOUTHERN BLOTTING, AS I UNDERSTAND, IS A TECHNIQUE WHERE AFTER YOU DO ONE OF THESE ELECTROPHORETIC SEPARATIONS THAT YOU DESCRIBED, YOU BLOT THE DNA OUT OF THAT GEL ONTO A MEMBRANE, AM

I RIGHT SO FAR?

A. YOU PROBABLY KNOW AS MUCH ABOUT IT AS I DO, BUT GO AHEAD. YES, YOU DO, THAT TECHNIQUE IS KIND OF OUT OF SKILL.

Q. BUT THAT TECHNIQUE THEN INVOLVES USING A LABELED PROBE, ONE OF THESE RADIOACTIVELY LABELED PIECES OF DNA TO STICK TO THE MEMBRANE IN CASES WERE THERE IS COMPLEMENTRY DNA THERE AND NOT STICK IN OTHER PLACES, IS THAT THE THEORY BEHIND THAT PROCEDURE?

A. YOU DON'T WANT IT TO STICK TO THE MEMBRANE, TO STICK TO THE DNA ITSELF.

Q. NOW, YOU INDICATED THAT TECHNIQUE IS A LITTLE OUT OF STILL, BUT IN 1983, 1984 THAT WAS A STANDARD BIOCHEMICAL THE TECHNIQUE, WASN'T IT?

A. YES. YES, IT STILL IS, I SPOKE A LITTLE SOON. THERE ARE PEOPLE THAT STILL DO SOUTHERN, IT'S NOT QUITE AS NECESSARY.

Q. AND IT WOULD BE A WAY OF IDENTIFYING MORE SPECIFICALLY WHAT IS IN ONE OF THESE BANDS ON THE GEL?

A. MORE SPECIFICALLY THAN WHAT?

Q. THAN JUST CHARACTERIZING BY THE SIZE.

A. YES.

Q. NOW, AS I RECALL, YOU YOURSELF HAD NOT DONE A SOUTHERN BLOT EXPERIMENT PRIOR TO 1983?

A. I MISSED THAT.

Q. IN FACT, AT LEAST UP TO THE TIME OF YOUR DEPOSITION I THINK YOU TOLD ME YOU HAD NEVER DONE THAT?

A. I DON'T LIKE THEM. I HAVE NOT DONE -- I HAVE NOT WITH MY

OWN HANDS. I SUPERVISED PEOPLE THAT HAVE DONE IT.

Q. DOCTOR, DO YOU STILL HAVE YOUR LABORATORY NOTEBOOKS UP THERE?

MAYBE YOU NEVER HAD THEM. I THINK MR. PASAHOW HAD THEM.

A. I DON'T THINK I HAVE THEM.

(PAUSE IN THE PROCEEDINGS)

MR. FIGG: I DON'T BELIEVE WE'RE INTRODUCING THE ORIGINAL NOTEBOOK INTO EVIDENCE, YOUR HONOR. PERHAPS IT WOULD BE EASIER FOR DR. MULLIS TO WORK WITH THE ORIGINAL RATHER THAN A COPY.

THE COURT: YES.

THE WITNESS: THIS IS LABORATORY NOTEBOOK NUMBER 1000 AND IT WAS THE ONE WHICH I USED IN AUGUST, I GUESS, 1982 THROUGH AUGUST 7TH 1984.

Q. THAT LABORATORY NOTEBOOK I BELIEVE DESCRIBES SOME OF THE EXPERIMENTS YOU WERE EXPLAINING TO MR. PASAHOW; IS THAT CORRECT?

A. I THINK THIS IS THE ONE THAT IS THERE IN. LIKE I SAID, I HAVEN'T HAD ACCESS TO THESE NOTEBOOKS MYSELF FOR SOMETIME UNTIL THIS TRIAL.

DO YOU WANT TO POINT OUT A PAGE IN PARTICULAR?

Q. NO. I JUST ASKED YOU IF THAT IS THE NOTEBOOK THAT CONTAINS YOUR EARLY EXPERIMENTS?

A. THAT WOULD BE THE ONE IT'S IN.

Q. THANK YOU.

I BELIEVE YOU TESTIFIED THAT THE FIRST EXPERIMENT THAT YOU DID THAT INVOLVED THE PCR REACTION OR ATTEMPTED PCR WAS IN SEPTEMBER OF 1983?

A. YES.

Q. AM I CORRECT THAT PRIOR TO THAT FIRST EXPERIMENT YOU HAD NEVER DONE A PRIMER EXTENSION REACTION WITH YOUR OWN HANDS?

A. I THINK THAT I REALLY -- I HAD NOT DONE ONE WITH MY OWN HANDS. IT'S HARD TO SAY HOW MUCH OF WHAT WAS GOING ON I TOUCHED. I WAS DEFINITELY SUPERVISING SOMEBODY WHO WAS DOING THAT AND I MAY HAVE ACTUALLY BEEN, YOU KNOW, FIT IN MORE THAN JUST VERBALLY INVOLVED, BUT I NEVER DONE ONE BY MYSELF WITH MY OWN HANDS.

Q. I'D LIKE TO GO THROUGH SOME OF THE EXPERIMENTS THAT YOU DESCRIBED FOR MR. PASAHOW IN A LITTLE MORE DETAIL.

(PAUSE IN THE PROCEEDINGS)

MR. FIGG: JUST FOR THE RECORD THE TEXT THAT WE'RE DEALING WITH IS A-51. DR. MULLIS IS WORKING WITH THE ORIGINAL, BUT IT HAS BEEN ENTERED AS EXHIBIT A-51.

Q. DOCTOR, I'VE PLACED ON THE OVERHEAD PROJECTOR A COPY OF WHAT I BELIEVE WE ESTABLISHED WAS PAGE 129 OR 122 OF YOUR NOTEBOOK. CAN YOU CONFIRM THAT -- WHICH ONE IT IS?

A. ON PAGE . . . IS THIS PAGE 983?

Q. PAGE 129, RIGHT?

A. OKAY.

Q. IS THAT THE FIRST PAGE OF YOUR LAB NOTEBOOK THAT DESCRIBES

WORK YOU DID WITH WHAT YOU NOW CALL PCR?

A. OBVIOUSLY, CALLED IT THAT RIGHT THERE ON THAT PAGE PCR01. POLYMERASE CHAIN REACTION NUMBER 01.

Q. THIS WAS AN EXPERIMENT THAT WAS IN DONE IN SEPTEMBER OF 1983?

A. YES.

Q. YOU INDICATED THAT YOU FIRST THOUGHT OF THIS PROCEDURE IN, I BELIEVE YOU SAID, APRIL OR MAY OF 1983?

A. I WASN'T REALLY SURE WHAT THE MONTH WAS, BUT IT COULD HAVE BEEN APRIL OR MAY. THE ONLY THING I REALLY REMEMBER DISTINCTLY THE CALIFORNIA BUCKEYES WERE IN BLOOM THAT'S WHERE I PLACED IT IN MY MIND.

MR. FIGG: LET ME ASK MS. MORIYAMA TO MARK THIS DOCUMENT AS THE NEXT EXHIBIT.

THE CLERK: PLAINTIFFS A-183 MARKED FOR IDENTIFICATION ONLY.

(PLAINTIFF'S EXHIBIT A-183 MARKED FOR IDENTIFICATION)

Q. (BY MR. FIGG) DOCTOR, CAN YOU IDENTIFY WHAT WE'VE MARKED AS EXHIBIT A-183?

A. IT LOOKS TO BE A COPY OF AN INVENTION DISCLOSURE. SOMETHING I WROTE UP DESCRIBING THE SORT OF FIRST -- THIS IS THE THING I WROTE UP FOR THE PATENT PEOPLE AT CETUS DESCRIBING THE INVENTION.

Q. THIS WAS A DOCUMENT THAT CETUS -- IT WAS NORMAL CETUS

PRACTICE FOR PEOPLE WHO THOUGHT THEY MADE PATENTABLE INVENTION TO WRITE UP SOMETHING CALLED AN INVENTION DISCLOSURE?

A. YES.

Q. ON THIS INVENTION DISCLOSURE ON PAGE THREE IT SAYS THE CONTINUED INVENTION WAS CONCEIVED ON JULY 1983. DO YOU NOW BELIEVE THAT WAS A MISTAKE?

A. WELL, I'M NOT -- YOU KNOW, IT'S REALLY FUZZY IN MY MEMORY. I ASSOCIATE THE DATES THE APRIL AND MAY WITH THE FACT THAT I REMEMBER BUCKEYES AND IT TURNS OUT IT'S NOT ALL THAT VERY IMPORTANT.

I HADN'T REALLY MADE A LOT OF EFFORT TO TRY TO FIGURE OUT EXACTLY WHAT DATE IT WAS I CONCEIVED IT ON.

Q. YOU BELIEVE IT WAS IN THE SPRING BECAUSE THE BUCKEYES WERE IN BLOOM?

A. THAT'S MY SORT OF MEMORY OF IT. IT COULD HAVE BEEN INTO JULY, THE BUCKEYES COULD HAVE COME FROM ANOTHER TRIP. I DON'T HAVE, YOU KNOW, I WASN'T -- IT'S NOT IMPORTANT, IS IT?

I MEAN, IS IT IMPORTANT?

Q. YOU'RE RIGHT. I DON'T THINK IT'S THAT IMPORTANT. I JUST WANT TO NAIL IT DOWN BECAUSE I'M WONDERING WHY YOU WAITED FROM APRIL UNTIL SEPTEMBER TO DO YOUR FIRST EXPERIMENT.

A. WELL, SINCE IT'S NOT IMPORTANT LET'S JUST SAY IT WAS JULY AND YOU WON'T HAVE THAT QUESTION.

Q. SO YOU DON'T RECALL ONE WAY OR THE OTHER?

A. I DON'T REALLY RECALL.

Q. DR. MULLIS, YOU DID THIS FIRST EXPERIMENT THAT'S DESCRIBED HERE YOU WERE TRYING TO AMPLIFY A SECTION OF DNA I BELIEVE FROM SOMETHING CALLED THE HUMAN NERVE GROWTH FACTOR GENE?

A. YES.

Q. AND THIS WAS THE REACTION THAT YOU SAID DID NOT WORK?

A. YES. I WAS UNABLE TO DETECT ANY REACTION PRODUCT.

Q. NOW, THIS SEQUENCE OF THIS GENE THAT YOU WERE WORKING WITH WAS SOMETHING THAT HAD BEEN PUBLISHED IN A SCIENTIFIC JOURNAL?

A. YES, IT HAD BEEN PUBLISHED IN NATURE I THINK BY GENENTECH.

Q. YOU DIDN'T HAVE TO DETERMINE THE SEQUENCE YOURSELF BEFORE BEGINNING THE EXPERIMENT?

A. NO, I DIDN'T.

Q. THE PRIMERS YOU USED WERE ONES THAT HAD BEEN MADE IN YOUR LABORATORY AT CETUS?

A. YES.

Q. AND YOU DECIDED ON THE LENGTHS OF THE PRIMERS TO USE IN THIS EXPERIMENT FROM YOUR KNOWLEDGE OF THEIR MELTING TEMPERATURES; IS THAT CORRECT?

A. WELL, I CERTAINLY HAD A -- HAD AN ESTIMATE OF WHAT THEIR MELTING TEMPERATURES WOULD BE FROM A COMPUTER PROGRAM I HAD IN WHICH THEY WERE WRITTEN.

I DON'T -- I'M NOT SURE EXACTLY WHETHER THAT'S WHAT GOT ME TO DECIDE ON THE LENGHTS. I DON'T SEE ANYWHERE WHERE IT SAYS THE LENGTHS WERE PICKED FOR ANY PARTICULAR REASON. AND I COULD HAVE PICKED THEM FOR LOTS OF DIFFERENT REASONS.

I CERTAINLY WOULD NOT HAVE PICKED SOME THAT WERE SO SHORT AS TO NOT FORM A STABLE DUPLEX AT THE TEMPERATURE THE EXPERIMENT I WAS CONTEMPLATING. I ALSO WOULD HAVE WANTED THEM TO BE LONG ENOUGH TO MAKE SPECIFIC CONTACTS WITH DNA, SO I -- I WOULD SAY THE SIZE WAS PROBABLY -- THERE WERE SEVERAL CONSIDERATIONS IN CHOOSING IT, BUT THAT WOULD HAVE BEEN PROBABLY THE MAJOR ONE.

THE MELTING TEMPERATURE IS CONNECTED WITH THE SPECIFICITY THAT'S ALWAYS AVAILABLE. ALL THOSE THINGS KIND OF WORK TOGETHER.

Q. IN ANY EVENT, THE MELTING TEMPERATURE WAS AN IMPORTANT FACTOR IN YOUR DECIDING WHAT LENGTH OF PRIMERS TO USE?

A. YES, IT WAS.

Q. YOU DETERMINED THE MELTING TEMPERATURE FROM A FORMULA YOU FOUND IN THE LITERATURE, IS THAT RIGHT? ONE BY SLICKER AND SHILL (PHONETIC)?

A. SLICKER AND SHILL, I SAW SEVERAL AND THAT'S ONE I HAD CHOSEN AT THE TIME.

Q. NOW, THIS EXPERIMENT WAS BEGUN AT AROUND MIDNIGHT; IS THAT RIGHT?

A. IT SAYS BEGUN AT 12:00 O'CLOCK MIDNIGHT. KIND OF DRAMATIC EXPERIMENT.

Q. WELL, ACTUALLY AN IMPULSIVE EXPERIMENT, JUST A SHOT TO SEE WHAT WOULD HAPPEN?

A. I DON'T KNOW IF WE WANT TO USE THAT WORD, MR. FIGG. JUST A

SHOT TO SEE WHAT WOULD HAPPEN I SUPPOSE.

Q. WELL, DO YOU RECALL I ASKED YOU THAT QUESTION IN YOUR DEPOSITION AND YOU TOLD ME IT WAS JUST TAKEN AS A SHOT IN A SENSE?

THE COURT: THAT'S WHAT HE JUST TESTIFIED TO.

THE WITNESS: I THINK SO. OBVIOUSLY, TOOK TIME TO WRITE IT DOWN. I ORDERED THE OLIGONUCLEOTIDES IN AUGUST, I STARTED THE EXPERIMENT IN SEPTEMBER, I THINK IT WAS A LITTLE MORE THAN JUST IMPULSIVE.

BUT IT WAS A SHOT AND THE CONDITIONS I WAS TRYING THIS AT IS WHAT I THOUGHT THAT IF EVERYTHING WORKS OUT EXACTLY RIGHT THEN THE EASIEST THING I WILL HAVE TO DO -- THE HARDEST THING I WILL HAVE TO DO IS PUT THOSE THINGS IN THERE, HEAT IT UP, COOL IT OFF OR WHATEVER AND GO HOME. THAT'S WHAT I DID. IF THAT HAD WORKED I'VE WOULD HAVE NEVER TRIED TO DO IT IN THE HARD WAY.

Q. SO THIS WASN'T REALLY THE KIND OF CYCLING REACTION THAT WE'VE BEEN TALKING ABOUT FOR THE LAST MANY DAYS, THIS WAS ONE WHERE YOU PUT EVERYTHING IN THE TUBE HAD A CONSTANT TEMPERATURE, LEFT IT THERE OVERNIGHT AND CAME BACK IN THE NEXT DAY TO SEE WHAT HAPPENED?

A. IT WASN'T A CYCLING REACTION IN THE WAY OF ME HAVING TO DO THE CYCLE. I WAS HOPING THAT SOMETIME DURING THE NIGHT THE OLD NUCLEOTIDES WOULD LAND ON THEIR TARGET AND BE EXTENDED AND THEN THE PRODUCTS WOULD COME OFF AND THEN OTHER OLIGONUCLEOTIDES WOULD COME BACK. ALL THE SAME PROCESS WOULD TAKE PLACE, BUT

TAKE PLACE WITHOUT ME HAVING TO SHIFT THE TEMPERATURE OR TAKE ANYTHING OUT. IT WAS A POSSIBILITY.

Q. I'M NOT DISPUTING THAT. I'M JUST ASKING YOU TO CONFIRM THAT THE EXPERIMENT WAS DONE THAT WAY. YOU PUT EVERYTHING IN THE TUBE, LEFT IT AT 37 DEGREES, THEN CAME BACK THE NEXT DAY TO SEE WHAT HAPPENED?

A. YES.

Q. SOMETHING REFERRED TO IN HERE IS BUFFER DELUXE, THAT'S THE BUFFER THAT YOU USED FOR PUTTING ALL OF THESE PRIMERS AND POLYMERASE AND SO FORTH IN?

A. YEAH, THAT WAS SOMEWHAT WHIMSICAL NAME FOR JUST A SOLUTION I MADE UP. I THINK IT TELLS YOU WHAT THE COMPOSITION OF IT IS THERE.

Q. I BELIEVE YOU GOT THAT BUFFER RECIPE FOR BUFFER DELUXE FROM A PAPER ON POLYMERASE OR FROM SOMEONE ELSE IN THE LABORATORY WHO WAS WORKING WITH POLYMERASE?

A. IT PROBABLY WAS SOMETHING -- I THINK THIS PARTICULAR FORMULATION OF IT MAY HAVE BEEN EXACTLY, YOU KNOW, I THINK I MENTIONED THIS EARLIER, I DID NOT HAVE A HABIT OF DOING THINGS EXACTLY.

COULD HAVE BEEN ANY KIND OF OVER A WIDE RANGE AND I MAY HAVE COPIED IT PRECISELY FROM SOMEONE ELSE OR I MAY HAVE JUST GOTTEN -- JUST MADE SORT OF A SHOT AT IT SORT OF LIKE SOMEBODY ELSE. I'M NOT REALLY POSITIVE, BUT THERE WERE LOTS OF RECIPES AVAILABLE FOR USING POLYMERASE IF THAT'S WHAT YOU'RE TRYING TO

GET AT AND I COULD HAVE EASILY PICKED UP ONE OF THOSE. I DIDN'T HAVE TO DO ANY DEVELOPMENT OR ANY EXPERIMENTS TO JUST LAND ON THIS.

Q. AND THERE'S SOMETHING ELSE IN HERE THAT IS REFERRED TO AS BSA AS I UNDERSTAND THAT WAS SOMETHING THAT WAS A KNOWN STABILIZER FOR ENZYMES?

A. YES. ESPECIALLY IF YOU WERE GOING TO USE AN ENZYME AS A FAIRLY LOW CONCENTRATION YOU WANT TO HAVE SOME OTHER PROTEIN IN THERE TO PROTECT THAT THE ENZYME WAS DEGRADATION BY THINGS THAT WOULD DEGRADE PROTEIN.

Q. OTHER PEOPLE IN THE LITERATURE HAVE DESCRIBED USING BSA AND POLYMERASE BUFFERS; IS THAT RIGHT?

A. YES. I THINK THAT'S LISTED AS ONE OF THE COMPONENTS OF BUFFER DELUXE.

Q. YES. DOCTOR, AM I CORRECT THAT FOR CERTAIN OF THE BUFFERS THAT YOU USED YOU GOT THE RECIPE OUT OF THE BIOLABS CATALOG?

A. YES. THE RESTRICTION IN THE NUCLEASE TYPE RECIPES I PROBABLY TOOK OUT OF THERE.

Q. ISN'T IT ALSO TRUE YOU TOOK SOME OF THE POLYMERASE BUFFER RECIPES OUT OF THE BIOLABS CATALOG?

A. I MAY HAVE. I'VE GOT A LOT OF RECIPES, YEAH, HERE'S ONE BIOLAB TO KLENOW.

Q. KLENOW IS A FORM OF DNA POLYMERASE?

A. YES.

Q. AND THE BIOLABS IS A COMPANY THAT SELLS ENZYMES LIKE DNA

POLYMERASE TO SCIENTISTS?

A. YES, IT IS.

Q. AND IN THEIR CATALOG THEY HAVE RECIPES FOR BUFFERS THAT THEY RECOMMEND FOR USING WITH THEIR ENZYMES?

A. YES.

Q. NOW, AM I CORRECT, DOCTOR, THAT YOU TESTED THESE, SOME OF THESE BUFFERS THAT YOU HAD ACCESS TO IN STRAIGHT PRIMER EXTENSION REACTIONS, NOT PCR, BUT STRAIGHT PRIMER EXTENSION REACTIONS?

A. YES, I DID SOME OF THAT.

Q. AND A BUFFER WORKED WELL IN A PRIMER EXTENSION REACTION, THEN THAT WOULD SUGGEST THAT IT MIGHT WORK WELL IN A PCR REACTION?

A. WELL, ALL OTHER THINGS BEING EQUAL, I THINK SO. THAT WAS THE PURPOSE PROBABLY FOR DOING THE PRIMER REACTION I THOUGHT WAS SORT OF A . . . IF THE BUFFER WOULD WORK FOR THAT THEN IT WAS A GOOD CHANCE TO BELIEVE IT WOULD WORK FOR WHAT I HAD IN MIND FOR IT.

Q. WHICH WAS ABOUT CR?

A. EXTENDING PRIMERS WITH POLYMERASE?

Q. YEAH. BUT YOU SAID IT WOULD WORK WELL FOR WHAT YOU HAD IN MIND FOR IT, WHAT YOU HAD IN MIND FOR IT WAS PCR?

A. I WOULD -- THAT'S WHAT I WOULD HAVE THOUGHT. THERE'S NO WAY TO PROVE IT AT THAT POINT. I WAS -- I WILL -- I'LL SAY I WAS EXPERIMENTING WITH POLYMERASE IN SYSTEMS THAT TO ME WERE SIMILAR

TO WHAT I WAS GOING TO NEED FOR PCR AND THAT BUFFERS THAT WORKED FOR THERE WOULD PROBABLY HAVE WORKED FOR PCR.

I DIDN'T REALLY THINK THE BUFFER WAS ALL THAT IMPORTANT.

Q. NOW, THIS REACTION THAT'S DESCRIBED IN PCR01 EXPERIMENT IS . . . HOW DID YOU PLAN TO ANALYZE THE RESULT OF THAT?

A. OF THAT EXPERIMENT?

Q. YEAH.

A. I THINK IN THAT EXPERIMENT I PLANNED TO PUT THE MATERIAL ON A GEL, PROBABLY AFTER LABELING IT BY DOING A LITTLE LONGER REACTION TIME WITH THE LABEL INCORPORATED MAYBE DOING -- MAYBE I WAS GOING TO HEAT IT WITH THE LITTLE LABELED DEOXY C OF THE C NUCLEOTIDE, INCORPORATE THAT INTO THE PRODUCT, PUT IT ON AN ELECTROPHORESIS GEL AND SEE IF I COULD SEE A 400 BASE PAIR WHICH IS WHAT THOSE TWO PRIMERS WOULD HAVE MADE ON THE HUMAN GROWTH FACTOR.

Q. SO THE PRIMARY DETECTION DETECT THAT YOU WERE PROPOSING HERE WAS TO SEE WHETHER THERE WOULD BE INCORPORATION OF RADIOACTIVELY LABELED C'S?

A. INTO A BAND OF 400 BASE PAIRS.

Q. RIGHT. AND YOU CONCLUDED YOU WERE UNABLE TO DETECT ANY SUCCESS IN THIS EXPERIMENT?

A. I COULD NOT SEE A BAND OF 400 BASE PAIRS THAT WAS RADIOACTIVE.

Q. DO YOU KNOW WHETHER TODAY WHETHER THIS EXPERIMENT WORKED OR

NOT.

LET ME REPHRASE THAT QUESTION.

DO YOU KNOW TODAY WHETHER THE AMPLIFICATION PART OF THIS EXPERIMENT WORKED?

A. IF IT HAD I WOULDN'T HAVE GONE TO A HARDER METHOD.

Q. BUT, IN FACT, IT WAS THE WAY THAT YOU SET UP THE DETECTION REACTION THAT CREATED SOME AMBIGUITY ON THAT, ISN'T IT?

A. THE REACTION HAD WORKED REALLY WELL THE DETECTION METHOD I SET UP WOULD HAVE PROBABLY WORKED WELL, TOO. IF THE REACTION WORKED ABOUT ONE MILLION OF A PERCENT, FOR INSTANCE, THE DETECTION METHOD I SET UP WOULD NOT HAVE DETECTED THAT.

THOSE KIND OF THINGS ARE -- IF I HAD INCREDIBLY SENSITIVE WAY OF DETECTING ONE MOLECULE WHICH I HAVE NOW BECAUSE OF PCR, I MIGHT HAVE DISCOVERED THAT THAT DID MAKE ONE MOLECULE. BUT WITH THE DETECTION SYSTEM I HAD I WOULD HAVE HAD TO MAKE PROBABLY FOUR, 500,000 COPIES OF THE MOLECULE IN ORDER TO SEE IT.

Q. AND YOU DIDN'T SEE THAT?

A. I DIDN'T SEE IT.

Q. THE NEXT EXPERIMENT YOU DID INVOLVING PCR -- EXCUSE ME, PCR IS THE EXPERIMENT WHICH YOU LABELED IN YOUR NOTEBOOK AS PCR02; IS THAT RIGHT?

A. YES, I THINK THAT'S TRUE.

Q. NOW, THIS EXPERIMENT WAS DONE DIFFERENTLY, IN THIS ONE YOU USED THE MULTIPLE CYCLES OF HEATING, COOLING AND PRIMER

EXTENSION, CORRECT?

A. YES, I FIGURED I WAS GOING TO HAVE TO DO IT.

Q. AND THIS EXPERIMENT YOU ADDED THE PRIMERS WHICH YOU DESIGNATED KM22 AND KM23 TO A MIXTURE; IS THAT RIGHT?

A. YES.

Q. AND YOU ADDED THE FOUR BUILDING BLOCKS OF DNA WHICH YOU CALLED THE DNTP HERE, RIGHT?

A. YES.

Q. AND YOU ADD HUMAN DNA, WHICH I GATHER IS THE SAMPLE OF WHOLE HUMAN DNA?

A. YES.

Q. YOU ADDED THE DNA POLYMERASE ENZYME WHICH IS INDICATED HERE AS THE KLENOW ENZYME?

A. WELL, I DON'T KNOW IF I ADDED THAT RIGHT AWAY.

Q. RIGHT. BUT THAT WAS PART OF THE REACTION MIXTURE THAT ULTIMATELY WAS USED?

A. THAT WOULD HAVE BEEN ADDED AFTER THE HEATING STEP.

Q. RIGHT. AND YOU USED YOUR BUFFER DELUXE AS THE MEDIUM FOR THIS REACTION?

A. YES, I DID.

Q. AND, AS YOU POINT OUT, YOU HEATED THESE -- THIS SOLUTION TO A HUNDRED DEGREES FOR TWO MINUTES?

A. YES.

Q. AND WHAT WAS THE PURPOSE OF THAT?

A. THAT WOULD BE DENATURE THE HUMAN DNA.

Q. IN OTHER WORDS, TO SEPARATE THE STRANDS?
A. YES.
Q. THEN YOU CHILLED IT ON ICE FOR TWO MINUTES, RIGHT?
A. IT SAYS TWO MINUTES CHILL ON ICE.
Q. RIGHT. THEN YOU ALLOWED IT TO COME BACK TO 37 DEGREES AND YOU ADDED YOUR ENZYME?
A. SAYS, WARM TO 37, THAT WOULD HAVE BEEN PUT IT IN A 37 DEGREE VAT AND ADD THE ENZYME.
Q. AND THE ENZYME THEN WOULD -- WHAT YOU WERE PROPOSING HERE WAS THE PRIMERS WOULD ANNEAL TO THE STRANDS OF THE DNA AND THE ENZYME WOULD THEN EXTEND THOSE STRANDS OUT?
A. YES.
Q. AND YOU WENT THROUGH THAT REACTION FOR TEN CYCLES?
A. WELL, LET'S SEE, IT SAYS . . . I THINK I DIDN'T DO IT EXACTLY. THE NEXT TIME I HEATED IT I ONLY HEATED IT FOR ONE MINUTE AND THEN IT SAYS . . . WARM TO 37, YEAH, PRETTY MUCH THE SAME THING, TEN TIMES.
Q. YOU USED A HUNDRED DEGREES FOR DENATURING THE DNA BECAUSE YOU HAD A BOILING WATER VAT AVAILABLE; IS THAT RIGHT?
A. BECAUSE -- WELL, A BOILING WATER VAT, I MADE ONE AVAILABLE SO I COULD DO THAT.
Q. BUT THAT WAS A TYPICAL WAY OF DENATURING DNA?
A. THAT WAS -- YES, A TYPICAL WAY OF DENATURING DNA.
Q. AND YOU USED 37 DEGREES FOR THE PRIMER EXTENSION PART OF THE REACTION BECAUSE THAT WAS A TRADITIONAL WAY TO RUN POLYMERASE

REACTIONS?

A. 37 DEGREES, YES.

Q. NOW, --

A. THERE WERE OTHER WAYS OF RUNNING THAT WERE ALSO TRADITIONAL. THAT'S NOT THE ONLY WAY THAT WAS TRADITIONAL.

Q. BUT 37 --

A. SOMETIMES 40 DEGREES, IT DEPENDS A LOT OF WHAT SORT OF -- WHAT OTHER FACTORS IN THE EXPERIMENT ARE. MY PROCEDURE IS 37.

Q. NOW, IN THIS REACTION YOU ADDED THE RADIOACTIVELY LABELED C'S IN A FINAL CYCLE; IS THAT CORRECT?

A. YES. IT SAYS PRIOR TO ADDITION NUMBER TEN MICROLITER OF APPROXIMATELY ONE MICROCURIE OF . . . DEOXY CTP WAS ADDED. OKAY.

Q. AND AGAIN HERE YOU COULD NOT DETECT SUCCESS IN THIS EXPERIMENT; IS THAT CORRECT?

A. IT IS CORRECT. I'M NOT SURE IF IT'S WRITTEN HERE OR JUST -- SOMEWHERE ELSE, BUT, IT'S TRUE.

Q. NOW, THIS -- IN THIS EXPERIMENT YOU WERE WORKING WITH WHOLE HUMAN DNA AND YOU ADDED THESE RADIOACTIVELY LABELED C'S TO THAT WHOLE HUMAN DNA MIXTURE IN ADVANCE OF THAT LAST CYCLE?

A. WELL, BY THE TIME WE GOT AROUND TO THE LAST CYCLE I DON'T KNOW HOW COLD THE DNA WAS. IT HAD BEEN HEATED QUITE A LOT. I ADDED THE RADIOACTIVE C'S TO THE MIXTURE RIGHT BEFORE, I FINISHED JUST SAYING THAT.

Q. YOU REALIZED, AT LEAST YOU LATER CONCLUDED, THAT THAT

DETECTION TECHNIQUE WAS NOT APPROPRIATE FOR WORKING WITH THE COMPLEX MIXTURE OF DNA LIKE THAT?

A. I THINK -- WELL, LET'S -- IF I HAD GOTTEN IN ENORMOUS A VERY NICE AMPLIFICATION THERE FIVE CYCLES I WOULD HAVE GOTTEN 32 TIMES. IF IT WAS EVERYTHING HAD RUN REALLY NICELY THAT SYSTEM MIGHT HAVE BEEN ABLE TO DETECT IT. I'M NOT SURE WHAT YOU MEAN BY THE FACT IT WAS NOT APPROPRIATE.

Q. AM I CORRECT THAT THERE ARE TWO POSSIBLE THINGS THAT MAY ACCOUNT FOR YOUR -- TWO GENERAL THINGS THAT MAY ACCOUNT FOR YOUR INABILITY TO SEE A SUCCESSFUL REACTION HERE, ONE IS THAT THE AMPLIFICATION REACTION DIDN'T WORK, THE OTHER IS THAT YOUR DETECTION PROCEDURE DIDN'T WORK?

A. THEY'RE BOTH CONNECTED.

Q. YEAH. AND AM I CORRECT THAT YOUR FAVORITE EXPLANATION FOR WHY YOU DIDN'T SEE SUCCESS IS THAT THE ANALYTICAL PROCEDURE DIDN'T WORK?

A. THAT'S MY FAVORITE EXPLANATION?

Q. YES.

A. I THINK AT THIS POINT LOOKING BACK ON IT, I COULD SAY THAT WAS A PERFECTLY -- THAT'S A REASONABLE EXPLANATION MY ANALYTICAL SYSTEM WAS NOT SUFFICIENT TO -- I MEAN, I CAN'T REMEMBER WHAT THAT GEL LOOKED LIKE. IT MIGHT HAVE BEEN THERE WAS RADIOACTIVITY ALL OVER THE PLACE.

I HAVEN'T LOOKED AT THIS EXPERIMENT FOR A LONG TIME AND I DON'T KNOW -- I MEAN, I'M NOT REALLY SURE WHAT THE GEL LOOKED

LIKE. IF I HAD THAT I COULD LOOK AT IT AND POSSIBLY SPECULATE ON IT. IT DIDN'T WORK. IF I HAD SEEN A 400 BASE PAIR PIECE I WOULD HAVE DEFINITELY WRITTEN IT DOWN THAT HERE.

Q. YOU CAN'T TELL TODAY WHETHER THE AMPLIFICATION REACTION WAS A FAILURE THERE OR WHETHER IT WAS JUST A FAILURE IN YOUR ABILITY TO DETECT BECAUSE OF THE DETECTION METHOD THAT YOU USED?

A. I CAN TELL THAT THE EXPERIMENT TO DETECT AMPLIFICATION WAS A FAILURE. I'M SURE THAT -- I MEAN, WHATEVER WENT ON IN THERE -- I MEAN, THE FACT THAT I COULDN'T DETECT IT -- I CAN'T REALLY SAY A LOT ABOUT WHAT HAPPENED. I CAN'T TELL THAT IT DIDN'T HAPPEN.

Q. THAT WAS MY QUESTION.

A. BUT . . . OKAY.

Q. AND JUST SO WE UNDERSTAND, THE REASON FOR THAT IS BY USING THAT DETECTION YOU WOULD HAVE BEEN LABELING LOT OF DIFFERENT FRAGMENTS OF DNA IN THAT MIXTURE OF DNA THAT YOU WERE USING?

A. THAT COULD HAVE BEEN THE EXPLANATION. IT ALSO COULD HAVE BEEN THAT -- I MEAN, IF WE COULD CELL THE GEL IT WOULD MAKE IT A LOT EASIER TO DETERMINE.

IF THE GEL WAS BLACK ALL UP AND DOWN THE LANE AND BAND HAVING BEEN THERE WOULD HAVE BEEN INVOLVED JUST TOTALLY COVERED WITH OTHER DNA THEN THAT WOULD HAVE BEEN THE EXPLANATION.

IN THE ABSENCE OF THAT GEL I'M NOT REALLY SURE WHETHER THERE WAS A LOT OF STUFF LABELED OR JUST NOTHING LABELED. THAT WAS NOT A DISTINCT BAND AT 400 LABEL OR I WOULD HAVE COMMENTED TO THAT EFFECT.

Q. NOW, IN THESE FIRST TWO EXPERIMENTS YOU WERE USING THIS MIXTURE OF HUMAN DNA OR WHAT YOU'VE REFERRED TO AS GENOMIC DNA. I RECALL YOU TELLING MR. PASAHOW YOU THEN DECIDED TO GO TO A DNA THAT WHAT WAS A SIMPLER TARGET REGION. DID I HEAR THAT CORRECTLY?

A. YES.

Q. THAT WAS A PLASMID DNA?

A. YES.

Q. THAT NEXT EXPERIMENT WAS DONE IN DECEMBER OF 1983; IS THAT CORRECT?

A. YES, THAT IS.

Q. THAT EXPERIMENT WAS ONE I BELIEVE YOU CALLED PCR175 BECAUSE THE BULK OF THE EXPERIMENT WAS DESCRIBED ON PAGE 175 OF YOUR NOTEBOOK?

A. YES, SIR.

Q. EXPERIMENT ACTUALLY BEGAN ON PAGE 173 OF YOUR NOTEBOOK?

A. THE DESCRIPTION OF IT ACTUALLY BEGAN ON PAGE 173.

Q. NOW, THIS EXPERIMENT THAT BEGINS ON PAGE 173 IS EXAMPLE 1 OF YOUR '202 PATENT?

A. YES, IT IS.

Q. IT'S EXAMPLE 1 OF YOUR '195?

A. YES, IT IS.

Q. AND THE TARGET YOU WERE LOOKING AT IN THIS EXPERIMENT WAS 45 BASES LONG OR 45 NUCLEOTIDES LONG?

A. THE TARGET WAS A 25 BASE PAIR FRAGMENT THAT WAS ON A 44 BASE

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PAIR RESTRICTION FRAGMENT.

Q. RIGHT. YOU CUT OUT A PIECE OF DNA THAT WAS 44, 45 LONG AND YOU WERE TRYING TO AMPLIFY 25 BASES OUT OF THAT 44, 45?

A. YES. THAT WAS ALSO IN A CONTEXT OF THE REST OF THE PLASMID IN THERE.

Q. AND YOU USED TWO PRIMERS HERE, ONE WAS 11 BASES LONG AND ONE WAS 13 BASES LONG?

A. YES, I DID.

Q. NOW, IN THIS ONE I BELIEVE YOU HEATED FOR ONE MINUTE TO DENATURE THE DNA?

A. IT SAYS HEAT TO 85 FOR ONE AND A HALF MINUTES. PROBABLY MEANT I INTENDED TO HEAT IT FOR ONE MINUTE, THEN I WENT OVER A LITTLE BIT BECAUSE I'VE WRITTEN IN A HALF WITH A PEN.

Q. PAGE 175 IS A PAGE THAT ACTUALLY DESCRIBES THE PROCEDURES THAT YOU USED, THE CONDITIONS THAT YOU USED?

A. RIGHT.

Q. AND YOU HEATED IT FOR ONE MINUTE BECAUSE, BASED ON WHAT YOU KNEW OF HYBRIDIZATION, IT WAS NOT UNREASONABLE TO EXPECT THIS 45 BASE FRAGMENT TO DENATURE IN A MINUTE OR A MINUTE AND A HALF, RIGHT?

A. RIGHT. I THINK I PROBABLY CALCULATED WHAT ITS MELTING TEMPERATURE SHOULD BE AND 85 WAS ABOUT ABOVE IT AND I THOUGHT THE MINUTE OR MINUTE AND A HALF SEEMS TO ME NOT VERY CRITICAL IN EITHER TIMES.

Q. IT'S NOT A CRITICAL CONDITION?

A. I DON'T THINK THAT A HALF MINUTE -- I WOULDN'T HAVE WANTED TO HEAT FOR JUST 30 SECONDS. I THINK I WOULD HAVE GONE FOR A LITTLE LONGER THAN THAT, BUT I WASN'T SURE.

Q. AND YOU HEATED TO 85 DEGREES BECAUSE YOU KNEW THAT THIS PARTICULAR DNA WOULD DENATURE AT 85 DEGREES?

A. I HAD PROBABLY LOOKED UP, I TRIED TO CALCULATE WHAT THE MELTING POINT OF THAT FRAGMENT WOULD BE. I COULD HAVE HEATED TO A HUNDRED, TOO. IT DIDN'T REALLY MATTER AT THAT POINT. I USE A CALCULATION SAYS IT MELTS, IT SHOULD HAVE MELTED AROUND 72.8 I THINK.

Q. AND IN THIS CASE THEN YOU COOLED IT DOWN TO 32 DEGREES TO GET THE PRIMERS TO ANNEAL TO THE TWO STRANDS AFTER THEY HAD BEEN SEPARATED BY HEATING?

A. YES.

Q. AND THEN YOU ADDED THE POLYMERASE ENZYME AND ALLOWED THE PRIMER EXTENSION REACTION TO PROCEED?

A. YES, I DID.

Q. AND YOU INDICATE DOWN HERE AT THE BOTTOM OF ALL OF THESE STEPS GO TO FIVE. THAT'S YOUR COMPUTER LANGUAGE JUST MEANING REPEAT THOSE CYCLES; IS THAT CORRECT?

A. YES.

Q. AND YOU USED A RATIO OF PRIMERS TO THE TEMPLATE HERE OF A THOUSAND TO ONE; IS THAT CORRECT?

A. YES.

Q. YOU USED 2,403 PICOMOLES OF EACH OF THE PRIMERS AND YOU USED

2.4 PICOMOLES OF THE MATERIAL YOU WERE TRYING TO AMPLIFY?
A. YES.
Q. AND WHEN YOU DESIGNED THIS EXPERIMENT YOU HAD PLANNED TO DO TEN CYCLES, RIGHT?
A. YES, I THINK THAT'S THE WHAT I PLANNED AND I THINK THAT'S WHAT I DID.
Q. AND YOU CHOSE A THOUSAND TO ONE RATIO OF PRIMERS TO THE TEMPLATE BECAUSE YOU KNEW THAT TWO TO THE TENTH POWER WAS ONE THOUSAND?
A. I THINK IT WAS -- THAT WOULD HAVE BEEN A REASONABLE, YOU KNOW, REASON TO DO IT, BUT I'M NOT POSITIVE THAT'S WHY I CHOSE IT. I KNEW THAT AND I CERTAINLY WANTED TO HAVE ENOUGH PRIMER IN THERE TO -- I DIDN'T WANT TO RUN OUT OF PRIMER AND THE REACTION WORKED A HUNDRED PERCENT TEN CYCLES I WOULD HAVE BEEN CLOSE.

IF I HAD GOTTEN IT TO WORK ANYWHERE NEAR A HUNDRED PERCENT FOR TEN CYCLES I WOULD HAVE BEEN PERFECTLY HAPPY. I WOULDN'T WORRY TOO MUCH ABOUT THOSE LAST -- IF IT WAS GOING A HUNDRED PERCENT I WOULDN'T WORRY ABOUT WHAT WOULD HAPPEN TO THE EIGHTH, NINTH, TENTH CYCLES.

Q. RIGHT. BUT YOU KNEW THAT THE PRIMERS WOULD BE INCORPORATED INTO THE NEW DNA AS IT WAS BEING MADE IN EACH CYCLE?
A. YES, I DID.
Q. NOW, THIS TIME YOU DID DETECT THAT THE REACTION WORKED; IS THAT RIGHT?
A. YES, I DID.

Q. THAT WAS THE GEL THAT MR. PASAHOW PROJECTED UP ON THE SCREEN?

A. YES.

Q. AND THAT GEL WAS . . . WELL, YOU FIRST ATTEMPTED TO DETECT IT WITH LIGHT OR JUST A VISUAL ESTIMATION?

A. YES, WITH THE VIDEO BROMIDE STAIN.

Q. THAT WAS THE ONE THAT MR. PASAHOW SHOWED YOU AND THE GEL DOESN'T SHOW UP VERY WELL ON MY PHOTOCOPIES, BUT THAT WAS WHERE YOU NOTICED THAT THE ARROW MARKS THE SPOT WHERE THE TRUE BELIEVER SEES THE BAND AT 24 BASE PAIRS?

A. YES.

Q. ACTUALLY YOU MISCOUNTED. IT SHOULD HAVE BEEN 25 BASE PAIRS, SHOULDN'T IT?

A. IT'S A MISTAKE YOU COULD MAKE EASILY ENOUGH.

Q. RIGHT. BUT WHEN YOU KNEW THAT YOU COULD THEN RUN THIS THROUGH ANOTHER CYCLE AND BY MEASURING THE INCORPORATION OF RADIOACTIVE C'S YOU WOULD HAVE MUCH MORE SENSITIVE WAY OF DETECTING WHETHER THE REACTION HAD WORKED OR NOT?

A. YES.

Q. AND IN THIS CASE THAT WORKED BECAUSE THE DNA WAS A MUCH LESS COMPLEX MIXTURE?

A. IT'S PROBABLE -- THAT CERTAINLY WAS -- THE FACT IT WAS LESS COMPLEX WAS INVOLVED IN MY DETECTION AND IT WOULD HAVE BEEN BECAUSE IT WAS LESS COMPLEX.

I'M REALLY -- WE WOULD BOTH BE SPECULATING EXACTLY WHY

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IT WORKED IT. IT DID WORK AND THE DNA WAS LESS COMPLEX.

Q. BUT YOU BELIEVE THE DETECTION WAS MORE RELIABLE HERE BECAUSE IT WAS A LESS COMPLEX MIXTURE?

A. RELIABLE?

IT WOULD BE EASIER TO DETECT -- IT'S EASIER TO DETECT THINGS WHEN THEY'RE NOT IN THE PRESENCE OF A LOT OF OTHER THINGS LIKE THEM. AND THIS SYSTEM WAS SIMPLE ENOUGH WHERE HOPEFULLY I DIDN'T HAVE A LOT OF OTHER THINGS, I HAD SORT OF CLEANER BACKGROUND; IN OTHER WORDS, TO SEE MY 25 BASE PAIRS THAN I PROBABLY HAD FOR THE FOUR HUNDRED BASE PAIRS IN THE HUMAN EXPERIMENT.

Q. HAVE YOU EVER TRIED TO DECIDE OR DETERMINE WHAT THE EFFICIENCY OF THIS REACTION WAS?

JUST ASKING IF YOU EVER MADE THAT CALCULATION.

A. I KNOW IT WAS NOT TERRIBLY EFFICIENT, BUT I'VE NEVER REALLY GONE BACK AND CALCULATED WHAT THE EFFICIENCY WAS AT THE TIME.

Q. BUT YOU DO CONSIDER THIS TO BE A SUCCESSFUL PCR REACTION?

A. I CONSIDER IT TO BE A SUCCESSFUL PCR REACTION, YES.

Q. AND YOU PUT IT IN YOUR PATENT AS AN EXAMPLE OF THE INVENTION YOU WERE CLAIMING?

A. YES, I DID. AS I MENTIONED BEFORE, I HAD A SENTIMENTAL ATTACHMENT TO IT ALSO AND IT BEING THE FIRST I THOUGHT IT WOULD MAKE A NICE FIRST EXAMPLE.

Q. NOW, WHEN YOU SAW THE GEL WITH THE RADIOACTIVE NUCLEOTIDE INCORPORATED, YOU BELIEVED THE REACTION WORKED WHEN YOU SAW THAT

BAND AT 25 BASE PAIRS, DIDN'T YOU?

A. WHEN I SAW THAT BAND COMING OUT OF THE BLUE AND IT WAS RIGHT WHERE I THOUGHT IT WOULD BE I WAS VERY HAPPY AND I THOUGHT IT WORKED. I WAS NOT CONVINCED ABSOLUTELY BEYOND ANY DOUBT, BUT I WAS PRETTY MUCH CONVINCED. IT'S EASIER TO BELIEVE IN YOUR OWN THINGS, TOO.

Q. I'M SORRY.

A. I KNEW IT WAS NOT CONVINCING EVIDENCE IN THE SENSE I COULDN'T HAVE TAKEN THAT EVIDENCE DOWN THE HALL TO SOMEBODY AND SAID, SEE, ABSOLUTELY WITHOUT A DOUBT PCR WORKS ON THE BASIS OF THIS. IT CERTAINLY CONVINCED -- IT WAS REALLY NICE RESULT TO GET. IT WAS INDICATIVE OF THE FACT THE PROCESS WAS GOING TO WORK.

Q. WELL, DO YOU STILL --

A. IT DIDN'T MAKE A TEN BASE PAIR FRAGMENT, IT MADE A 25 BASE PAIR FRAGMENT.

Q. YES. AND DO YOU STILL HAVE THE SCIENTIFIC AMERICAN ARTICLE UP THERE THAT YOU DISCUSS WITH MR. PASAHOW?

A. YES. I THINK . . .

(PAUSE IN THE PROCEEDINGS)

THE WITNESS: YES, THE UNUSUAL ORIGIN OF THE POLYMERASE CHAIN REACTION.

Q. (BY MR. FIGG) RIGHT. THAT'S EXHIBIT A-52. ON PAGE 64 OF THIS ARTICLE YOU INDICATED THAT, IN THE THIRD COLUMN AT THE TOP, WHEN EVERYTHING WAS READY I RAN MY FAVORITE KIND OF EXPERIMENT

ONE INVOLVING A SINGLE TEST TUBE. WOULD PCR AMPLIFY THE DNA SEQUENCE I HAD SELECTED, THE ANSWER WAS YES.

SO AT LEAST WHEN YOU WROTE THIS ARTICLE YOU FELT THAT THE REACTION WORKED?

A. YES.

Q. DR. MULLIS, DID YOU, IN THIS REACTION, DID YOU INCLUDE ANY EXPERIMENTS WHERE THE PRIMERS WERE NOT INCLUDED?

A. IT WAS A ONE TUBE EXPERIMENT, MR. FIGG. IT SAYS MY FAVORITE KIND OF EXPERIMENT INVOLVING A SINGLE TEST TUBE AND PRODUCING A YES OR NO ANSWER.

Q. BUT MY QUESTION WAS MORE SPECIFIC THAN THAT. DID YOU RUN AN EXPERIMENT ALONGSIDE WHERE YOU DIDN'T INCLUDE PRIMERS?

A. I HAD ABSOLUTELY NO CONTROLS IN THIS EXPERIMENTS.

Q. SO THE ANSWER IS, NO, YOU DID NOT?

A. THE ANSWER IS NO, I DID NOT.

Q. AND DID YOU, AND SIMILARLY YOU DIDN'T RUN ANY EXPERIMENTS WHERE YOU DIDN'T CONCLUDE THE TEMPLATE STRAND OR THE TEMPLATE DNA?

A. NO, I DID NOT. IF I CAN BE ALLOWED TO SAY THIS. I DIDN'T RUN ALL THOSE EXPERIMENTS. INSTEAD I RAN OTHER PCR EXPERIMENTS TO FINALLY CONVINCED MYSELF THAT THE PROCESS WORKED.

IF THIS WERE THE LAST EXPERIMENT I EVER DONE I WAS COMING IN HERE TELLING YOU I HAD DONE THAT AND THEREFORE I HAD DONE PCR, THEREFORE, I WOULD FEEL KIND OF FOOLISH. AS IT TURNS OUT I DON'T.

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Q. YOU NEVER WENT BACK AND RAN THOSE EXPERIMENTS EITHER, DID YOU?

A. I DON'T THINK ANYBODY IS GOING TO BE INTERESTED IN THAT 25 BASE PAIR FRAGMENT AGAIN EITHER. IT'S AN EXPERIMENT TO GET A SIMPLE YES OR NO ANSWER. THE ANSWER IS, YES, I WENT ON TO THE NEXT EXPERIMENT WHICH WAS TO TRY TO PROVE THAT THE PROCESS DID WORK AND TO EXPLORE ITS FEATURES.

Q. WHEN YOU WROTE YOUR INVENTION DISCLOSURE THAT I HANDED TO YOU EARLIER YOU LISTED THAT EXPERIMENT AS YOUR FIRST REDUCTION TO PRACTICE; IS THAT CORRECT?

YOU CAN LOOK AT THE DOCUMENT.

A. YES, IT WAS.

Q. AND WHEN YOU -- WHEN WE SAY YOUR FIRST REDUCTION TO PRACTICE IN TERMS OF AN INVENTION DISCLOSURE, THAT MEANS THE FIRST TIME THAT YOU SUCCESSFULLY PERFORMED THE EXPERIMENT THAT IS THE SUBJECT OF THE INVENTION WHICH YOU WANTED TO PATENT TO BE WRITTEN FOR?

A. THAT'S THE FIRST TIME THAT I FELT THAT I HAD SUCCESSFULLY REDUCED IT TO PRACTICE, YES.

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

A. YES, I DO.

(PAUSE IN THE PROCEEDINGS)

Q. (BY MR. FIGG) WOULD YOU REFER TO CLAIM 1 OF THAT PATENT. I'VE PLACED A COPY, A BLOW UP OF IT UP HERE ON THE EASEL.

A. OKAY.

Q. AM I CORRECT AS YOU READ IT, CLAIM 1 LITERALLY COVERS RUNNING TWO REACTIONS CYCLES?

A. IT DESCRIBES -- YES, IT DESCRIBES TWO REACTION CYCLES.

Q. SO IN THAT SENSE CLAIM 1 IS CONSIDERABLY BROADER THAN THE EXPERIMENT THAT YOU DESCRIBED IN PCR175, WHICH IS EXAMPLE 1 OF YOUR PATENT?

A. IN THE SENSE THAT THE CLAIM REFERS TO AT LEAST TWO. IN OTHER WORDS, I'M NOT -- IT'S BROADER, IT WOULD INCLUDE, TEN, 15, 20, WHATEVER.

Q. OR INCLUDE TWO?

A. OR INCLUDE TWO. IF YOU JUST DO TWO YOU'RE UNDER THIS CLAIM.

Q. AND CLAIM 2 ADDS ONE MORE CYCLE AND REQUIRES NO MORE THAN THREE CYCLES TOTAL?

A. YES, CLAIM 2 EXPANDS ON IT.

Q. NOW, DOCTOR, LOOKING AT CLAIM 1, HOW LONG CAN THE PRIMERS BE OR WHAT CAN THE LENGTH OF THE PRIMERS BE AND STILL BE ENCOMPASSED BY THE LANGUAGE OF CLAIM 1 AS YOU UNDERSTAND IT?

A. THE PRIMERS HAVE TO BE OF SUCH A LENGTH THAT THEY WILL CAUSE PRIMER EXTENSION PRODUCTS TO BE MADE ON TEMPLATES WHICH THEMSELVES CAN BE ACTING AS TEMPLATES FOR THE NEXT CYCLE.

THE REACTION HAS TO WORK. IF THE REACTION WORKS IN THE WAY IT'S EXPLAINED HERE THEN THEY WERE THE RIGHT SIZE.

Q. ANY PRIMER THAT WILL WORK IS ENCOMPASSED BY YOUR CLAIM?

A. ANY PRIMER THAT WILL WORK IN SUCH A WAY AS THE LANGUAGE OF THIS CLAIM DESCRIBES AND THERE IS HELP, IN FACT, IN CHOOSING

PRIMERS AND THE SPECIFICATION OF THE PATENT. THE CLAIM HAS TO BE INTERPRETED THE WAY I UNDERSTAND IT. THAT'S WHAT THE REST OF THE PATENT IS FOR, IS TO TRY TO HELP YOU WITH THAT.

THE CLAIM IS ONE SENTENCE IT'S HARD TO SAY EVERYTHING ABOUT SOMETHING IN ONE SENTENCE, BUT IF THE PRIMER WORKS IN ACCORDANCE WITH THIS CLAIM THEN THAT'S THE RIGHT LENGTH.

Q. THAT'S IT?

A. IF IT WILL DO WHAT THE CLAIM SAYS IT NEEDS TO DO THEN IT'S ALL RIGHT.

Q. AND THE SAME IS TRUE WITH THE AMOUNT OF PRIMER, THIS CLAIM DOESN'T REQUIRE ANY SPECIFIC AMOUNT OF PRIMER, DOES IT?

A. THE SAME THING APPLIES FOR THE AMOUNTS AND FOR ALL OF THE PARAMETERS THAT YOU MIGHT WANT TO GO THROUGH. IF, IN FACT, THOSE THINGS ARE CHOSEN SO THAT THE ELEMENTS OF THIS CLAIM ARE ALL FULFILLED, THEN THAT'S OKAY.

Q. IF SOMEBODY FINDS A CONDITION THAT WORKS, IF THEY FIND A PRIMER CONCENTRATION THAT WORKS, WHETHER IT'S DESCRIBED IN YOUR PATENT OR NOT, THAT PARTICULAR CONCENTRATION, THEN IN YOUR VIEW IT'S COVERED BY THE CLAIM?

A. MY VIEW ACTUALLY NOT REALLY THAT IMPORTANT, I DON'T THINK, IN DECIDING IT. BUT, YES, THAT'S MY UNDERSTANDING OF THE WAY THE PATENT WORKS.

Q. NOW, YOU INDICATED TO MR. PASAHOW THAT THE MOST IMPORTANT PARAMETER WAS THE ANNEALING TIME. WHAT KIND OF ANNEALING TIME IS --

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A. WAIT. I DIDN'T DO THAT. I SAID VERY CLEARLY THAT ALL PARAMETERS ARE REALLY RELATED TO EACH OTHER. IF YOU GET YOUR ANNEALING TIME WAY OFF THEN THAT IS THE MOST IMPORTANT, THAT'S WHY YOU DIDN'T GET IT TO WORK.

IF YOU GET YOUR ANNEALING TIME RIGHT AND SOME OTHER THING WRONG THEN THAT'S THE MOST IMPORTANT THING. JUST IN THE CONTEXT OF A GIVEN EXPERIMENT, YOU KNOW, WHEN YOU SAY IT'S THE MOST IMPORTANT, IT'S NOT THE ONLY ONE AND IF YOU MESS UP THE REST OF THEM AND YOU GET YOUR ANNEALING TIME RIGHT THEN YOU STILL DON'T GET, YOU KNOW, THERE'S NO PRODUCT.

Q. DOCTOR, YOU SPENT SOMETIME TALKING WITH MR. PASAHOW ABOUT THE IMPORTANCE OF ANNEALING TIME IN EVENT AND ALL I WANT TO ASK YOU IS WHAT SORT OF ANNEALING TIME IS SPECIFIED IN CLAIM 1?

A. THAT SORT OF ANNEALING TIME WHICH WILL ALLOW THE ELEMENTS OF THAT CLAIM TO BE PRACTICED AS THEY'RE DESCRIBED. WHATEVER ANNEALING TIME WORKS.

Q. AND HOW WOULD, IF A PERSON IS READING YOUR PATENT AND WANTS TO DO A NEW PCR EXPERIMENT THAT'S NEVER BEEN DONE BEFORE, HOW WOULD THAT PERSON KNOW WHAT ANNEALING TIME WORKS?

A. THEY'LL LOOK IN THE EXAMPLES AND THEY'LL SEE THAT THOSE ARE SOME THAT HAVE WORKED AND THEN THEY'LL START FROM THERE. AND IF THEY WANT AN EXPERIMENT WITH THEIR OWN ANNEALING TIMES AFTER THAT -- I MEAN, THAT'S A PLACE FOR THEM TO START.

Q. WELL, IF THEY LOOKED AT EXAMPLE 1 THEY WOULDN'T LEARN ANYTHING ABOUT ANNEALING TIMES, WOULD THEY?

A. THEY MIGHT NOT. I DON'T KNOW, LET'S LOOK AT IT.

(PAUSE IN THE PROCEEDINGS)

THE WITNESS: WELL, THEY'D KNOW I'M NOT TALKING ABOUT TWO OR THREE HOURS. IT SAYS THE MIXTURE IS HEATED TO 85 DEGREES FOR FIVE MINUTES AND ALLOWED TO COOL TO THE TEMPERATURE. IT DOESN'T SAY SLOW COOLED TO AMBIENT TEMPERATURE. SAYS ALLOWED TO COOL TO AMBIENT TEMPERATURE.

WHAT MY INTERPRETATION OF THAT WOULD BE TO THAT, YOU KNOW, I'M NOT CONCERNED ABOUT A MINUTE HERE OR A MINUTE THERE. TAKE IT OUT OF THE HOT VAT AND LET IT COOL, THAT'S HOW YOU INTERPRET IT.

Q. YOU DESCRIBED A PROCEDURE TO MR. PASAHOW WHERE YOU SAID MOST PEOPLE WERE TURNING OFF THE HEAT AND LETTING THE DNA STAY IN THE HOT WATER VAT AND LETTING IT SLOWLY COOL DOWN?

A. I SAID THAT'S WHAT MOST PEOPLE WERE DOING, BUT THE REST OF THIS PATENT -- LET'S DON'T TAKE LITTLE PIECES OUT OF CONTEXT AND START SAYING THIS IS THE ONLY THING THERE.

IF YOU LOOK THROUGH THE EXAMPLES OF THIS PATENT IT'S INTRODUCING A FAIRLY NOVEL APPROACH TO THAT AND THIS PARTICULAR EXAMPLE, IN THIS PARTICULAR EXAMPLE I DIDN'T HAPPEN TO PUT IN THIS PROCESS MIGHT TAKE 30 SECONDS OR A MINUTE. BUT IN OTHER OF THESE EXAMPLES I DID NOT SINGLE ONE OF THEM.

TALKS ABOUT WAITING AN HOUR OR ANY OF THAT STUFF BUT IN FACT AS I EXPLAINED AS I WAS TALKING TO MR. PASAHOW THAT WAS PRETTY MUCH THE COMMON PRACTICE.

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Q. SOME OF YOUR EXAMPLES SAY THAT YOU SHOULD COOL THE REACTION DOWN QUICKLY, BUT EXAMPLE 1 JUST SAYS ALLOW IT TO COOL.

NOW, IF EVERYONE WAS USING THIS PROCEDURE OF LETTING IT TAKE A LONG TIME TO COOL DOWN, HOW WOULD THEY KNOW THAT'S NOT WHAT YOU MEANT WHEN YOU SAID ALLOW TO IT COOL?

A. FROM READING THIS ONE EXAMPLE I DON'T THINK THEY WOULD HAVE KNOWN REALLY. THEY WOULD HAVE LOOKED AT A FEW OTHER EXAMPLES. WE HOPE A PERSON OF AVERAGE DILIGENCE OR WHATEVER TRYING TO REPEAT MY WORK WOULD HAVE READ THE WHOLE PATENT. THEY WOULDN'T HAVE PICKED OUT ONE EXAMPLE AND SAID, HEY, SEE IF I CAN GET THIS TO WORK.

Q. THE REST OF YOUR PATENT THAT COMES BEFORE THE EXAMPLES DESCRIBES THE GENERAL PROCEDURE FOR HOW TO CARRY OUT THE REACTION; IS THAT RIGHT?

A. YES, I BELIEVE THAT'S TRUE. IT DOES, NICE DIAGRAMS AND, YOU KNOW, I THINK IT'S A FAIRLY WELL WRITTEN PATENT.

Q. BUT THAT PART OF THE PATENT WHERE YOU'RE DESCRIBING THE GENERAL PROCEDURES AND WHAT'S IMPORTANT TO THE REACTION YOU NEVER MENTIONED ANNEALING TIME IN THERE?

A. WELL, THERE'S A LOT OF THINGS THAT I'VE LEFT OUT OF THIS PATENT, IT'S NOT AN EXHAUSTIVE, YOU KNOW, THE EXAMPLES AS DESCRIBED IN HERE WILL WORK AND THAT'S GOT ANNEALING TIMES IN IT.

IF I DIDN'T TALK ABOUT ANNEALING TIMES IN ONE OF THESE PARAGRAPHS THEN MAYBE WHILE I WAS WRITING THIS I COULD HAVE LEFT

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IT OUT OR MAYBE I JUST DIDN'T FEEL LIKE WRITING. THERE'S NO REAL LAW THAT SAYS YOU HAVE TO WRITE EVERYTHING IN EVERY PLACE, MR. FIGG.

THERE'S ENOUGH INFORMATION IN THIS PATENT WHERE SOMETHING COULD HAVE TAKEN THE PATENT AND GOTTEN THE PROCESS TO WORK.

Q. IF SOMEONE WAS WORKING WITH A NEW DNA THAT IS NOT DESCRIBED IN YOUR PATENT, THEY WOULD HAVE TO EXPERIMENT TO FIND OUT WHAT ANNEALING TIME TO USE, ISN'T THAT CORRECT?

A. NO, I DON'T THINK SO, MR. FIGG. I THINK THEY COULD HAVE TAKEN ANY PARTICULAR IN A SEQUENCE AND PROBABLY -- AND SUBSTITUTED THAT FOR THE SEQUENCE THAT'S DESCRIBED IN ONE OF THESE EXAMPLES AND THEY PROBABLY GOTTEN TO IT WORK RIGHT OFF THE BAT.

Q. IF THEY COME TO EXAMPLE 1 FIRST, THE VERY FIRST EXAMPLE IN YOUR PATENT, THEY MIGHT HAVE USED ONE OF THESE LONG ANNEALING TIMES?

A. I DON'T REALLY SEE WHERE EXAMPLE 1 TEACHES A LONG ANNEALING TIME. I -- THERE'S SOME OTHER EXAMPLES THAT DO SPECIFY ANNEALING TIME. THAT ONE DOESN'T SAY ANY TIME. JUST SAYS COOL IT DOWN AMBIENT TEMPERATURE. HOW LONG DOES THAT TAKE?

IF I HAD PUT IN COOL IT DOWN AND WAIT AN HOUR THAT WOULD HAVE PROBABLY INDICATED TO SOMEBODY THAT THERE'S SOMETHING GOING ON THERE THAT TAKES TIME. I JUST SAID COOL TO AMBIENT TEMPERATURE.

Q. DOCTOR, LET'S GO TO A DIFFERENT SUBJECT. YOU'VE ALREADY INDICATED THAT YOU DIDN'T THINK EXAMPLE 1 WAS A HUNDRED PERCENT EFFICIENT. DO YOU RECALL THAT?

A. I AM ABSOLUTELY CERTAIN IT WASN'T A HUNDRED PERCENT EFFICIENT.

Q. YOU TESTIFIED TO MR. PASAHOW THAT EXAMPLE TEN, I BELIEVE IT WAS, DESCRIBES A REACTION THAT WAS 60 PERCENT EFFICIENT?

A. I TESTIFIED THAT WHEN WE TOOK THE POINTS THAT WE GOT TAKING THE BANDS PUTTING THEM IN THE STIMULATION FLUID, WE TOOK THOSE POINTS PUT THEM INTO A COMPUTE PROGRAM AND THAT WOULD TAKE THAT KIND OF DATA AND MATCH IT TO AN EXPONENTIAL CURVE. THAT'S WHAT THE COMPUTE PROGRAM SAID.

IT SEEMED REASONABLE THE AVERAGE YIELD THROUGHOUT WAS ABOUT 62 PERCENT. IT DIDN'T REALLY SAY THE YIELD AT ANY ONE STEP WAS ANY PARTICULAR THING. WE ASSUMED THE YIELD WAS PROBABLY DROPPING A LITTLE AS THE REACTION WENT ALONG.

Q. SOMEONE DOES A REACTION TODAY WHAT SORT OF EFFICIENCY DO THEY HAVE TO REALIZE TO BE ENCOMPASSED BY THE LANGUAGE OF CLAIM 1?

A. WHATEVER EFFICIENCY IS REQUIRED FOR THEM TO DETECT THAT THEY'VE DONE PCR. I THINK IF THEY DO IT IN A WAY SUCH THAT NO ONE COULD TELL THEY WERE DOING PCR, THEN I DON'T THINK THEY WOULD BE ENCOMPASSED BY THAT CLAIM.

IF THEY ARE DOING PCR THEN THEY ARE -- IF THEY CAN DETECT THEY'RE DOING IT, THEN THEY HAVE TO BE DOING IT WITH AN

EFFICIENCY SUFFICIENT TO PRODUCE -- SORRY, SUFFICIENT TO PRODUCE SOME SORT OF EVIDENCE THAT THEY ARE DOING IT.

Q. AM I CORRECT THAT THE CLAIM COVERS REACTIONS WITH EFFICIENCIES ALL THE WAY DOWN TO THE POINT WHERE THE SYNTHESIS IS JUST ABOVE THE RATE OF DEGRADATION OF THE DNA?

A. I THINK WHEN I TALKED TO YOU BEFORE, I SAID THAT IN TERMS OF THAT'S THE LOWER LIMIT. IF, IN FACT, YOU'RE NOT MAKING MORE THAN BEING DESTROYED YOU'RE NOT -- REGARDLESS OF HOW SENSITIVE YOUR DETECTION METHODS AT THE END, YOU WON'T BE ABLE TO DETECT THAT YOU DID IT. SO I SAY THAT'S ONE SAY TO STATE IT.

I THINK THE BEST WAY TO STATE THAT WOULD BE TO SAY IF YOU CAN -- IF YOU RUN THE REACTION IN SUCH A WAY YOU CAN TELL THAT THE REACTION WORKED, THEN YOU'RE DOING PCR.

AND IF YOU RUN IT IN SUCH A WAY YOU CAN'T TELL THAT IT WORKED, THEN YOU CAN'T TELL WHETHER YOU'RE DOING PCR. SO I WOULD NOT, YOU KNOW, COME DOWN AND KNOCK ON YOUR DOOR AND SAY, HEY, YOU'RE DOING PCR.

Q. AM I CORRECT THAT IF YOU DO THE REACTION WITHOUT THE TARGET DNA IN THERE AND YOU GET NO AMPLIFICATION AND THEN YOU DO IT AGAIN WITH THE TARGET IN THERE AND YOU GET AMPLIFICATION, THEN THAT IS PCR AND THAT'S WHAT'S COVERED BY THIS CLAIM?

A. WHAT DO YOU MEAN BY AMPLIFICATION? YOU SAY, YOU GET AMPLIFICATION?

Q. GET MORE DNA THAN YOU STARTED WITH.

A. A DETECTABLE AMOUNT MORE THAN YOU STARTED WITH?

Q. YES.
A. IF IT'S DECTABLE IN ANY KIND OF RELIABLE METHOD, I WOULD SAY THAT SOUNDS LIKE WHAT I'VE BEEN SAYING OVER AND OVER AGAIN.
THE COURT: MR. FIGG, IT'S PAST OUR HOUR.
MR. FIGG: OKAY.
THE COURT: SO WE'LL HAVE TO RECESS AT THIS POINT.
HOW LONG DO YOU THINK YOU'LL BE WITH DR. MULLIS TOMORROW?
MR. FIGG: PROBABLY ANOTHER HOUR, ROUGHLY.
THE COURT: SO YOU KNOW ACCORDINGLY THEN IN TERMS OF SCHEDULING. FINE.
LADIES AND GENTLEMEN, HAVE A VERY PLEASANT AFTERNOON. PLEASE PUT YOUR THINGS TO THE SIDE AND WE'LL BE HAVING A JURY IN HERE FOR MUCH OF THE TIME YOU'RE OT HERE IN THE AFTERNOON. SO IF YOU'LL LEAVE THEM IN SOME NEAT ARRANGEMENT, HOWEVER MS. MORIYAMA HAS WORKED OUT WITH YOU. WE'LL SEE YOU TOMORROW MORNING AT 8:00 CLOCK. THANK YOU VERY MUCH.
YOU MAY STEP DOWN.
(WITNESS EXCUSED)
(PROCEEDINGS HELD IN OPEN COURT, JURY NOT PRESENT:)
THE COURT: ANYTHING WE NEED TO TAKE UP OR WE'LL JUST PROCEED TOMORROW?
MR. PASAHOW: WE HAVE SOME AN EXHIBIT TO ADMIT FROM THE EXAMINATION.
THE COURT: AN EXHIBIT TO AMEND?

MR. PASAHOW: TO ADMIT.

THE COURT: OKAY.

MR. PASAHOW: OR OFFER FOR ADMISSION.

THE COURT: OKAY.

MR. PASAHOW: IT'S EXHIBIT 178 WHICH WAS THE POSTER OF THE PARAGRAPH FROM THE NIH GRANT APPLICATION THAT WE USED YESTERDAY.

THE COURT: NO OBJECTION?

MR. FIGG: NO OBJECTION.

(DEFENDANT'S EXHIBIT B-178 RECEIVED IN EVIDENCE)

THE COURT: ADMITTED.

THE CLERK: B-178?

MR. PASAHOW: YES, I'M SORRY.

THE COURT: ANYTHING ELSE?

MR. LEWIS: YOUR HONOR, I WANTED TO REPORT WE HAVE CONSULTED ABOUT THE EXHIBITS THAT WE HAVE BEEN DISCUSSING.

MR. FIGG: WE'VE GOT SOME ROUTINE ONES I CAN OFFER RIGHT NOW IF -- WE MIGHT WANT TO GO AHEAD WITH THAT.

THE COURT: ALL RIGHT.

MR. FIGG: A-51 WHICH IS DR. MULLIS' NOTEBOOK ONE THOUSAND, AND A-183 WHICH IS THE INVENTION DISCLOSURES.

THE COURT: ANY OBJECTION?

I'M NOT SURE MR. PASAHOW HEARD THAT.

MR. FIGG: I'M SORRY. I'M OFFERING A-51 DR. MULLIS'

BOOK ONE THOUSAND AND A-183.

MR. PASAHOW: NO OBJECTION.

THE COURT: ADMITTED.

(PLAINTIFF'S EXHIBITS A-51 & A-183 RECEIVED IN EVIDENCE)

MR. PASAHOW: I SHOULD OFFER B-247 WHICH IS THE CHART OF THE PUBLICATIONS.

THE COURT: ANY OBJECTION?

MR. FIGG: NO, YOUR HONOR, NO OBJECTION.

THE COURT: ADMITTED, B-247.

THE CLERK: B-247 INTO EVIDENCE?

THE COURT: YES.

(DEFENDANT'S EXHIBIT B-247 RECEIVED IN EVIDENCE)

MR. LEWIS: YOUR HONOR, I'M SORRY I INTERRUPTED EARLIER. I WANTED TO REPORT WE HAVE CONSULTED ABOUT THE EXHIBITS WE HAD DISCUSSED BEFORE, THE TWO TIME LINE CHARTS AND THE THREE EXHIBITS THAT WE HAD THOUGHT COULD BE ADMITTED WITHOUT FURTHER TESTIMONY. AND I REGRET TO SAY WE HAVE NOT MADE ANY PROGRESS ON AGREEMENT ON THOSE.

THE COURT: WELL, ARE YOU PREPARED TO HAVE ME DEAL WITH THOSE NOW OR SOMETHING ELSE WE NEED --

MR. FIGG: I THINK WE CAN DEAL WITH IT NOW, YOUR HONOR.

THE COURT: DEAL WITH IT QUICKLY.

OKAY. WITH RESPECT TO THE TIME LINES THESE ARE THE

SAME PROBLEMS WE HAD BEFORE, RIGHT?

MR. LEWIS: YES, YOUR HONOR.

THE COURT: THEY'RE TIME LINES AND YOU'RE OBJECTING?

MR. LEWIS: THAT'S CORRECT.

THE COURT: WELL, IF ANY PORTIONS -- IF SOME PORTIONS OF THE TIME LINES WERE REDACTED, WOULD THAT MAKE A DIFFERENCE?

MR. LEWIS: YES. THERE ARE SPECIFIC PORTIONS THAT WE HAD OBJECTIONS TO.

THE COURT: WOULD THAT MAKE A DIFFERENCE TO YOU SO YOU WITHDRAW THE EXHIBIT THEN.

MR. NEWLAND: WELL, NO, WE DON'T, YOUR HONOR, FIND THE OBJECTION -- THE EXHIBITS REALLY TO BE OBJECTIONABLE. EXHIBIT A-157 THIS TIME LINE MR. LEWIS' OBJECTION IS TO THE WORD OBVIOUSNESS IN THE REASON THAT CETUS FILED THE TERMINAL DISCLAIMER AND THAT WAS IN FACT OVERCOME AND OBVIOUS REJECTION OF THE PATENT OFFICE.

MR. LEWIS: YOUR HONOR, THERE'S BEEN NO TESTIFY ABOUT THAT AND THE FILES THEMSELVES REFLECT THE OBJECTION WAS FILED TO OVERCOME A PROVISIONAL DOUBLE -- OBVIOUSNESS TYPE DOUBLE PATENTING REJECTION NOT AN OBVIOUS REJECTION, THOUGH, ARE TERMS OF ART.

THE COURT: INSTEAD OF MY SEARCHING FOR THE COPY, MAY I HAVE THE COPY OF THE TIME LINE?

MR. NEWLAND: HE HAS A COPY YOU CAN USE.

MR. LEWIS: WE'RE TALKING ABOUT THE ENTRY UP IN THE

UPPER RIGHT-HAND CORNER?

MR. NEWLAND: RIGHT.

(PAUSE IN THE PROCEEDINGS)

THE COURT: WELL, FIRST OF ALL, TO AMEND IT TO INDICATE IF, IN FACT, YOUR, MR. LEWIS, YOUR REPRESENTATION REGARDING THE RECORD IS ACCURATE, I THINK WOULD CONFUSE THE JURY --

MR. LEWIS: WELL, YOUR HONOR, FOR INSTANCE --

THE COURT: -- VERY, VERY MUCH.

MR. LEWIS: IF IT READ SOMETHING LIKE THE TERMINAL DISCLAIMER FILED I HAVE NO QUARREL WITH THAT.

THE COURT: THAT'S WHAT I WAS THINKING. WE JUST TAKE OUT THE REASONS FOR IT.

MR. NEWLAND: HE WANTS TO OVERCOME AN OBVIOUS REJECTION, YOUR HONOR, IT'S IN THE FILE WRAPPER OF THE APPLICATION THAT'S INVOLVED IN THIS PATENT IN SUIT.

THE COURT: WHAT DO YOU HAVE -- PASS IT UP.

MR. NEWLAND: YOUR HONOR, THAT'S A PORTION OF CETUS' RESPONSE IN ONE OF THE APPLICATIONS THAT REFERRED TO THE '195. THE EXAMINER WAS MAKING A REJECTION THAT THE CLAIMS IN THE APPLICATION WERE OBVIOUS OVER CLAIMS IN APPLICATIONS WHICH MATURED INTO THE '202 PATENT.

THE COURT: UH-HUH.

MR. NEWLAND: THE OBJECTION WAS OBVIOUSNESS.

MR. LEWIS: YOUR HONOR, I CAN POINT YOU TO THE PAGE WHERE THE EXAMINERS OBJECTION WAS MADE.

THE COURT: PAGE 0171? WELL, IT APPEARS THAT YOU'RE BOTH RIGHT, CORRECT?

MR. LEWIS: YOUR HONOR, 471, IF I'M LOOKING AT THE SAME DOCUMENT, IS NOT PART OF THE EXAMINERS . . .

MR. NEWLAND: I THOUGHT SHE SAID 171.

THE COURT: YES, 171. REJECTED PROVISIONALLY UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUS TYPE DOUBLE PATENTING, ET CETERA, AND ALSO AS BEING OBVIOUS OVER PENDING APPLICATION, ET CETERA.

MR. LEWIS: THE REJECTION ITSELF, YOUR HONOR, THAT WAS ADDRESSED . . . IS ON --

THE COURT: PAGE 177.

MR. LEWIS: I BELIEVE IT IS ON PAGE 157. THIS IS IN THE EXAMINERS ACTION, AS OPPOSED TO CETUS' FILING THE REJECTION ITSELF IS ON PAGE 157. IT REFERS TO A PROVISIONALLY REJECTION CLAIMS UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS TYPE DOUBLE PATENTING.

THE COURT: BUT THIS --

MR. NEWLAND: AND IF YOU READ ON.

THE COURT: THIS JANUARY 12TH RELATES TO --

MR. NEWLAND: THAT'S ACTUALLY THE TEXT OF CETUS' RESPONSE TO THE REJECTION AND EXPLAINS WHY THEY FILED THE TERMINAL DISCLAIMER.

MR. LEWIS: YES, IT WAS TO OVERCOME THE OBJECTION THAT WAS STATED ON PAGE 1357, WHICH IS NOT A SIMPLE OBVIOUSNESS

REJECTION UNDER 103. IT IS UNDER THE JUDICIALLY RELATED DOCUMENT OF OBVIOUSNESS TYPE DOUBLE PATENTING WHICH IS A DISTINCT TYPE OF REJECTION.

THE COURT: HOW DO YOU EXPLAIN THE PARAGRAPH AT THE MIDDLE OF THE PAGE ON 171?

MR. LEWIS: BECAUSE THAT, YOUR HONOR, IS NOT THE ONE THE TERMINAL DISCLAIMER WAS FILED TO ADDRESS.

IF YOU LOOK DOWN AT THE PARAGRAPH 11 WHERE IT SAYS PROVISIONAL REJECTION FOR OBVIOUSNESS TYPE DOUBLE PATENTING, AND YOU'LL SEE IN THAT PARAGRAPH, IN THE SECOND PARAGRAPH IN RESPONSE TO THAT REJECTION A TERMINAL DISCLAIMER IS BEING FILED.

THE COURT: OKAY. WAS IT ONLY AS TO THAT REJECTION?

MR. LEWIS: YES, THAT'S THE ONLY THING A TERMINAL DISCLAIMER WILL CURE, THAT TYPE OF REJECTION. IT WILL NOT CURE AN OBVIOUSNESS OBJECTION. THAT'S WHY WE'RE DOUBLING OVER THIS TERMINOLOGY, YOUR HONOR.

THE COURT: I WILL ALLOW THE TIME LINE IN. IT'S GOING TO READ TERMINAL DISCLAIMER FILE PERIOD OR YOU CAN WITHDRAW THE EXHIBIT, WHICHEVER, WHICH DO YOU WANT?

MR. NEWLAND: I THINK THE FORMER, YOUR HONOR.

THE COURT: OKAY. THEN IT'S ADMITTED WITH THAT REDACTION TO BE MADE.

(PLAINTIFF'S EXHIBIT A-157 RECEIVED IN EVIDENCE)

THE COURT: OKAY. WHAT'S THE NEXT ONE?

MR. NEWLAND: THE NEXT ONE IS ANOTHER TIME LINE EXHIBIT A-148.

THE COURT: WHAT'S THE PROBLEM WITH THAT ONE?

MR. NEWLAND: CETUS' PROBLEM WITH THIS ONE IS WHERE IT REFERS TO CETUS OBTAINING NSF GRANT. THAT'S THE WORD GRANT IS, I THINK, THE CRUX OF THIS ARGUMENT HERE.

MR. LEWIS: THERE'S MORE TO IT THAN THAT.

MR. NEWLAND: HERE WHERE PRECISELY THE LANGUAGE THAT CETUS USED IN THEIR PRESENTATION TO THE PATENT OFFICE DURING THE RE-EXAMINATION WHERE THEY TOLD THE PATENT OFFICE THAT THEY HAD RECENTLY RECEIVED DR. KHORANA'S GRANT. AND I THINK HERE WE'RE BEING AS PRECISE AS CETUS WAS IN THEIR PRESENTATION.

THE COURT: WHERE IS THE --

MR. NEWLAND: THERE'S A PETITION FILED --

THE COURT: GRANT OR GRANT APPLICATION?

MR. NEWLAND: SAYS GRANT DOCUMENTS, YOUR HONOR, IN THIS PETITION THAT CETUS FILED VERY LATE IN THE RE-EXAMINATION PROCEEDINGS.

THE COURT: DO YOU HAVE IT?

WHAT IS THE OBJECTION TO THE TERM GRANT, MR. LEWIS?

MR. LEWIS: NO, YOUR HONOR, THE OBJECTION STARTED OUT --

MR. NEWLAND: IF YOU LOOK AT THE UNDERLINED TEXT, YOUR HONOR.

MR. LEWIS: THIS DOCUMENT WAS USED WITH MR. DE GRANDI,

HE'S THE ONLY ONE WHO'S TESTIFIED ABOUT IT, AND ON LOOKING AT THE LATER EVEN FURTHER DOWN THE TIME LINE ABOUT THE PATENT OFFICE'S RESPONSE HE TESTIFIED SOLELY BASED ON HEARSAY.

IN FACT, YOUR HONOR SUSTAINED THE HEARSAY OBJECTION TO WHAT HE WAS SAYING ABOUT THAT. THAT'S ALL THAT WAS OFFERED IN SUPPORT AT THE TIME.

THE REASON THAT'S OF SOME IMPORTANT TO US, IMPORTANCE TO US, IT HAS TO DO WITH THIS OTHER DOCUMENT THE ENTRY MR. NEWLAND WAS TALKING ABOUT, ABOUT CETUS GETTING THE SUBPOENAED KHORANA NSF GRANT DOCUMENT. THAT'S WHAT MR. DE GRANDI SAID THAT TURNED OUT TO BE HEARSAY, TOO. IT'S WHAT DU PONT'S LAWYERS TOLD HIM.

WHAT WAS ACTUALLY RECEIVED AT THAT POINT WAS NOT THE FINAL GRANT, NOT THE ONE YOUR HONOR HAS MOVED, HAS ALLOWED IN TO EVIDENCE AS A PRINTED PUBLICATION. IT WAS A BUNCH OF DRAFTS OF THINGS THAT DO NOT EVEN ENJOY THE SAME STATUS AND DID NOT RAISE THE SAME QUESTIONS. AND I HAD PROPOSED THAT THIS BE MODIFIED SO THAT IT SAID CETUS GETS DRAFTS, BUT DU PONT DOESN'T WANT TO DO THAT. BUT AS IT STANDS NOW IT IS SUGGESTING A STATE OF FACTS THAT SIMPLY DOES NOT EXIST.

IN THE EXHIBIT B-24, WHICH I THINK IS THE SAME ONE THAT YOU'RE LOOKING AT, YOU CAN SEE ON PAGE 1 OF THE INFORMATION DISCLOSURE STATEMENT IT TALKS ABOUT RECEIVING THE DOCUMENTS FROM M.I.T. PURSUANT TO A SUBPOENA.

IT'S OBVIOUSLY WE'RE NOT GETTING IT FROM THE GRANTING

AGENCY, WHICH IS THE SAME AS THE THING THAT'S BEING DISCUSSED HERE, THE COPY IN THE GRANTING AGENCY. IF YOU LOOK OVER ON PAGE 2 AT THE VERY BOTTOM OF THE PAGE . . . WE APOLOGIZE FOR THE QUALITY OF THE GRANT DOCUMENTS, THE HANDWRITTEN NOTES AND NUMBERS THAT APPEAR THROUGHOUT, THEY APPEAR BECAUSE THEY'RE DRAFTS AND THAT'S WHAT WE'VE GOTTEN AT THAT POINT. SO TO DESCRIBE THEM AS GETTING IN THIS WAY WE I THINK IS PREJUDICIAL AND MISLEADING.

THE COURT: MAY I SEE THE TIME LINE EXHIBIT?

MR. NEWLAND: YOUR HONOR, IF I CAN -- I CAN ACTUALLY SHOW YOU THE DOCUMENTS THAT CETUS SENT TO THE PATENT OFFICE. THEY ARE SIGNED COPIES OF THE GRANT DOCUMENTS.

THE COURT: WELL, AS I UNDERSTAND IT THEY WERE THE GRANT APPLICATIONS AND THEN IT SOUNDS LIKE SOME OTHER PAPERS AS WELL.

MR. LEWIS: YOUR HONOR, WE SUBMITTED A DRAFT -- WE SUBMITTED THREE DOCUMENTS THAT WERE PRODUCED BY M.I.T. ONE OF THEM WAS A VERSION OF WHAT'S BEEN ADMITTED HERE AS THE NSF GRANT APPLICATION THAT HAD INTERLINEATION AND ADDITIONAL COMMENTS AND NOT ALL THE SIGNATURES. SO WE THINK IT'S A DRAFT, CLEARLY.

ANOTHER ONE WAS WHERE TWO DOCUMENTS THAT RELATED TO GRANTS BY THE NATIONAL CANCER INSTITUTE, THE NATIONAL INSTITUTES OF HEALTH AND THERE EXACT STATUS IS UNCLEAR IN TERMS OF WHETHER THEY WERE DRAFTS OR WHETHER THEY WERE FILE COPIES OR SOMETHING LIKE THAT.

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BUT THEY'RE NOT THE SIGNIFICANT DOCUMENTS HERE EITHER. IT'S THAT NSF GRANT PROPOSAL THAT CLEARLY IS A DRAFT BECAUSE IT HAS INTERLINEATIONS AND NOT A COMPLETE SET OF SIGNATURES THAT REALLY THE SIGNIFICANT ONE IN TERMS OF WHAT THIS EXHIBIT SAYS.

MR. NEWLAND: YOUR HONOR, I CAN SHOW YOU THE EXHIBITS.

THE COURT: I SEE THE CHARACTERIZATIONS OF THEM IN THE PETITION. THERE'S NO QUESTION THERE ARE HANDWRITTEN NOTATIONS ON THEM, RIGHT?

MR. NEWLAND: YES, YOUR HONOR,

THE COURT: AND THEY MAY NOT BE WHAT WAS ACTUALLY SUBMITTED AS A FINAL APPLICATION TO NSF, RIGHT?

MR. NEWLAND: I THINK THEY ARE THE SAME DOCUMENTS THAT WERE ACTUALLY SUBMITTED.

THE COURT: HOW DO WE KNOW THAT?

MR. LEWIS: YOUR HONOR, IF I MIGHT POINT OUT, THE COPY THAT DU PONT GOT FROM NSF DOESN'T CONTAIN THOSE THINGS. IT DOESN'T HAVE THOSE HANDWRITTEN NOTES ON INTERLINEATIONS.

THE COURT: WHAT WILL HAPPEN IS, IF YOU WANT THIS EXHIBIT IT WILL READ AS FOLLOWS:

WITH RESPECT TO THE NSF GRANT, FIRST OF ALL, THAT'S MISLEADING. IN ANY EVENT, IT SOUNDS LIKE SOMEBODY GOT A GRANT, WE DON'T EVEN HAVE THAT IN EVIDENCE AND WHAT IS REFERRED TO HERE ARE THE --

MR. NEWLAND: GRANT DOCUMENTS.

THE COURT: -- DOCUMENTS RELATED TO NSF GRANT

APPLICATION. THAT'S IT. OKAY.

MR. NEWLAND: OKAY, YOUR HONOR THE --

THE COURT: IT'S EASY TO RESOLVE IF YOU REALLY WANT TO. OR IF YOU HAVE TO I GUESS.

WHAT ELSE DO WE HAVE ADMITTED SUBJECT TO THOSE MODIFICATIONS. WHAT ELSE DO WE HAVE?

MR. LEWIS: THERE WERE --

MR. KURZ: YOUR HONOR, IF I COULD ADDRESS THIS ONE?

THE COURT: YES.

MR. KURZ: THIS IS EXHIBIT A-34 WHICH IS CERTAIN EXCERPTS FROM DOCTOR MOLINEUX' SUMMARIES. THERE WAS TESTIMONY BOTH ON DIRECT AND CROSS ABOUT THESE SUMMARIES.

THE COURT: UH-HUH.

MR. KURZ: AND DOCTOR MOLINEUX TESTIFIED THAT HE PREPARED THESE SUMMARIES AND SUBMITTED THEM TO DR. KHORANA AT HIS REQUEST.

I WOULD SUBMIT THESE SUMMARIES MEET THE REQUIREMENTS OF THE BUSINESS RECORDS EXCEPTION AND SHOULD BE ADMITTED. AND THIS IS JUST ONE EXCERPT, THESE ARE -- PAGES 15 THROUGH 28, 7,115, 7,028.

THE COURT: MR. PASAHOW.

MR. PASAHOW: YES, YOUR HONOR, THESE ARE ANOTHER VERSION OF PART OF THE PAGES THAT ARE IN EXHIBIT A-174. IF ONE LOOKS AT THE ORIGINAL YOU SEE THAT'S DIFFERENT WRITING INSTRUMENTS. I BELIEVE ONE IS A CARBON COPY THEN SOMEBODY HAS

WRITTEN IN WITH A PEN ON TOP IN HANDWRITTEN INTERLINEATIONS AND THE ONLY DIFFERENCE ARE THESE INTERLINEATIONS THAT HAVE BEEN ADDED ON THE EXHIBITS THAT'S NOW PROPOSED.

THE ADDITIONS APPARENTLY WERE MADE, OBVIOUSLY WERE MADE AT SOME TIME AFTER EXHIBIT 174 WAS PREPARED AND GIVEN TO DR. KHORANA. EXHIBIT 174 IS THE COPY THAT WAS OBTAINED FROM M.I.T. BY A SUBPOENA.

HAD THIS NEW EXHIBIT BEEN OFFERED IN A TIMELY WAY I WOULD HAVE CROSS-EXAMINED DOCTOR MOLINEUX ABOUT THESE ADDITIONS BECAUSE WE THINK THEY WERE PLAINLY ADDED AT SOME TIME AFTER THE DOCUMENT WAS PREPARED AND SUBMITTED TO ITS INTENDED RECIPIENT BECAUSE NO SUCH EXHIBIT EVEN EXISTED AT THAT TIME AND YOUR HONOR HAD RULED INADMISSIBLE THE EXHIBIT THAT CONTAINED IT. WE DID NOT GO INTO THAT ON CROSS-EXAMINATION.

MR. KURZ: YOUR HONOR, I BELIEVE THAT MR. PASAHOW DOESN'T HAVE THIS QUITE RIGHT. THE DOCUMENTS ARE DIFFERENT DOCUMENTS. MANY PAGES ARE DIFFERENT.

MR. PASAHOW DID CROSS-EXAMINE THE WITNESS EXTENSIVELY ON THE PAGES THAT WE'RE TALKING ABOUT OF A-34. I'M NOT SURE IF HE HAS THE EXACT SAME THING I DO.

THIS IS THE A-34 PAGES. I THINK THE ONES WITH THE NOTES ON TOP HAVE ALREADY BEEN ADMITTED.

THE COURT: ARE YOU LOOKING AT THE SAME PAGES OF THE SAME DOCUMENT?

MR. FIGG: YOUR HONOR, MAY I COMMENT ON THIS?

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THE COURT: ONLY IF IT WILL STRAIGHTEN MATTERS OUT.

MR. PASAHOW: THE INTERLINEATION I THINK WE HAVE NOW DETERMINED WAS ADDED AFTER EXHIBIT A-174 WAS PROVIDED TO DR. KHORANA.

MR. KURZ: YOUR HONOR, THESE ARE DIFFERENT DOCUMENTS, THAT'S ALL THERE IS TO IT.

MR. PASAHOW: THIS IS THE SAME PAGE.

MR. KURZ: OVERALL THE DOCUMENTS ARE DIFFERENT.

THE COURT: DO YOU THINK YOU CAN GET IT STRAIGHTENED OUT?

MR. PASAHOW: WELL, I DON'T KNOW THAT WE CAN, YOUR HONOR. WE CAN CERTAINLY TELL YOUR HONOR WHETHER THE PAGES ARE THE SAME OR DIFFERENT BECAUSE I THINK AS WE LOOK AT THESE PAGE BY PAGE WE WILL FIND THERE IN A DIFFERENT ORDER THAN ONE OR THE OTHER.

BUT THAT THE EXHIBIT IN EVIDENCE A-147 HAS THE ONLY ADDITIONAL PAGES, THAT IS THAT THE EXHIBIT IN EVIDENCE IS MORE COMPLETE IN TERMS OF HAVING PAGES THAT ARE NOT IN NOW WHAT'S BEING OFFERED, BUT WHAT IS NOW BEING OFFERED IS DIFFERENT IN TERMS OF ADDITIONAL MATERIAL ONLY IN TERMS OF THESE INTERLINEATIONS.

MR. KURZ: THAT'S NOT CORRECT.

THE COURT: THEN IT'S NOT A-174.

MR. FIGG: WE HAVE BASIC MISUNDERSTANDINGS BETWEEN US.

THE COURT: YOU STRAIGHTEN IT OUT BECAUSE I'VE GOT

ANOTHER TRIAL AT 2:00 O'CLOCK.

MR. PASAHOW: YES, YOUR HONOR, WE WILL DO THAT.

THE COURT: ANYTHING ELSE THAT NEEDS TO BE STRAIGHTENED OUT?

MR. LEWIS: I'M SORRY TO SAY IT, YOUR HONOR, BUT THERE WERE THREE EXHIBITS THAT WE HAD -- THAT CETUS HAD OFFERED THAT WE WERE GOING TO CONSULT ABOUT AND SEE IF WE COULD REACH AGREEMENT ON, AND WE DID NOT. B-87, B-88, I THINK YOU RECALL WHAT THOSE WERE.

THE COURT: YEAH.

MR. LEWIS: B-124. IT OCCURRED TO ME, YOUR HONOR, THAT AS REFLECTED IN WHAT WE FILED, B-124 IS PROBABLY NOT THE RIGHT DOCUMENT IN YOUR SET OF THE BINDERS. AS DU PONT KNOWS THIS. WE'VE STRAIGHTENED IT OUT WITH THEM, BUT I THINK WE FORGOT TO GIVE YOU A COPY.

THE COURT: WHAT IS B-24?

MR. LEWIS: IT'S THE CHART.

THE COURT: IS THAT CHART NOT A PART OF ONE OF THE OTHER EXHIBITS OR IS THAT A DIFFERENT CHART?

MR. LEWIS: IT IS A PART OF B-87.

THE COURT: SO B-87 WOULD BE ADMITTED YOU WOULDN'T NEED TO WORRY ABOUT IT?

MR. LEWIS: THAT'S CORRECT.

THE COURT: 124, RIGHT?

MR. LEWIS: YES.

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THE COURT: I THINK THEY'RE THE SAME. I'VE THINK I HAVE THE RIGHT EXHIBITS.

ARE YOU OFFERING IN ALL OF B-87?

MR. LEWIS: THAT WAS THE OFFER, YOUR HONOR.

THE COURT: FOR EXAMPLE, WHAT ARE THE JURORS GOING TO DO WITH THE FIRST THREE PAGES?

MR. LEWIS: I WOULD NOT INTEND TO ASK THEM TO DO ANYTHING.

THE COURT: I WOULDN'T EITHER.

MR. LEWIS: THERE ARE TWO PAGES OF TEXT THAT ARE OF PARTICULAR INTEREST TO US.

THE COURT: LET'S FIND OUT WHAT IT IS YOU REALLY WANT TO HAVE ADMITTED. LET'S NOT ADMIT THE REST OF THIS BECAUSE I THINK IT WILL ONLY SERVE TO CONFUSE THEM OR THEY MAY HAVE THE GOOD SENSE TO IGNORE IT ALTOGETHER.

MR. LEWIS: IF I -- I'LL CONFIRM THIS WITH MR. PASAHOW, BUT THE PAGES THAT I BELIEVE ARE OF PARTICULAR INTEREST TO US START AT D504216.

THE COURT: 216?

MR. LEWIS: YES. AND 217.

THE COURT: WHAT IS YOUR OBJECTION TO THESE EXHIBITS NOW?

MR. LEWIS: AND, OF COURSE, THE CHART, YOUR HONOR, WHICH IS 504224.

MR. KURZ: YOUR HONOR,

THE COURT: IS THERE ANY QUESTION ABOUT THESE COMING FROM DU PONT FILES?

MR. KURZ: NO, THERE'S NO QUESTION THEY CAME FROM DU PONT FILES. OUR PROBLEM IS THEY WERE -- THEY WERE, I GUESS, PRODUCED IN CONNECTION WITH INTERROGATORIES REGARDING THE INFRINGEMENT ISSUES.

NOW, THEY'RE BEING OFFERED ON TOTALLY DIFFERENT ISSUES. THEY WERE AUTHENTICATED AS DU PONT DOCUMENTS. WE'RE NOT DENYING THEY'RE DU PONT DOCUMENTS.

THE COURT: IT'S STILL AUTHENTIC.

MR. KURZ: IT'S AN AUTHENTIC DOCUMENT. YOU CAN SEE WHAT THE PROBLEM IS IN A SENSE WHAT THE JURY GOING TO DO WITH THIS. THERE'S NO TESTIMONY, THERE'S NO EXPLANATION TO WHAT IT IS.

THE SAME PROBLEM WITH BOTH 87 AND '88 BASICALLY THAT'S THE PROBLEM WITH HEARSAY TYPE DOCUMENTS IS THAT THERE'S NO ONE TO EXPLAIN IT. THE JURY IS JUST GOING TO GET THIS COLD WITHOUT ANY KIND OF EXPLANATION AT ALL ACCEPT FOR ONE THAT MIGHT BE OFFERED IN CLOSING ARGUMENT PERHAPS.

IT'S PATENTLY UNFAIR FOR THE JURY TO HAVE THE DOCUMENT WITHOUT THE BENEFIT OF TESTIMONY AND EXPLANATION.

MR. LEWIS: WELL, YOUR HONOR, FIRST OF ALL, IT'S NOT HEARSAY. IT'S PART OF THE ADMISSION WHICH BY DEFINITION IS NOT HEARSAY. BUT IF DU PONT HAS A PROBLEM WITH IT THEY CAN ALWAYS CALL A WITNESS TO TRY TO EXPLAIN IT IN THEIR REBUTTAL CASE AND

WE'LL BE HAPPY TO CROSS-EXAMINE.

THE COURT: WHAT ARE YOU GOING TO DO WITH THIS IN TERMS OF CLOSING ARGUMENTS?

MR. LEWIS: I THINK WE WOULD WANT TO POINT OUT TO THE JURY THAT IN DU PONT'S OWN DOCUMENTS THEY TALK ABOUT THE IMPORTANCE OF THE ADVANCE OF PCR IN CONNECTION WITH SECONDARY CONSIDERATIONS THAT ARE RELATED TO OBVIOUSNESS AND PRAISE THE PCR PROCESS.

AS TO THESE PARTICULAR PAGES, I THINK THE ONLY OTHER THING WE POINT OUT DU PONT ITSELF RECOGNIZED THERE WAS AN EXPLOSION IN THE LITERATURE AFTER THE USE OF PCR. THERE'S NOT A WHOLE LOT MORE TO IT THAN THAT.

MR. KURZ: YOUR HONOR, WE DON'T EVEN KNOW -- WE DON'T EVEN KNOW WHO THE AUTHOR IS OF THIS DOCUMENT. IT'S THE RANKEST FORM OF HEARSAY.

THE COURT: IT'S NOT HEARSAY. IT'S ONLY ONE FORM OF HEARSAY. DOESN'T HAVE TO BE RANK TO BE HEARSAY.

MR. KURZ: THIS IS -- IT'S CLEARLY A PROBLEM FOR US BECAUSE THERE'S NO --

THE COURT: THAT'S THE POINT OF IT, RIGHT?

THEY WOULDN'T INTRODUCE ANY EVIDENCE IF IT WASN'T GOING TO CREATE A PROBLEM FOR YOU AND VICE VERSA.

MR. KURZ: IT CREATES A PROBLEM FOR OUR CASE AND IT'S AN IMPORTANT PROBLEM. IT IS A HEARSAY DOCUMENT THAT'S IN DIRE NEED OF EXPLANATION BY A WITNESS AND I DON'T -- I DON'T THINK

IT'S AN ADMISSION.

THE COURT: MY PROBLEM IS THE PROBATIVE VALUE OF IT JUST SORT OF THROWN OUT THERE WITHOUT SOME ABSENCE OF A BETTER WORD FOUNDATION OR EXPLANATION OF IT BY SOMEONE. YOU KNOW, WHERE DID THIS COME FROM.

AND DU PONT IS A LARGE COMPANY, WHAT DEPARTMENT, WHAT WAS OBVIOUSLY -- IT'S NOT HEARSAY AS FAR AS I'M CONCERNED, BASED UPON WHAT I'VE HEARD SO FAR, BUT IT'S SORT OF JUST THROWN OUT THERE WITHOUT ANY EXPLANATION TO WHO AUTHORED IT AND SO FORTH.

AND I HAVE NO DOUBT WHAT YOU ATTEMPT TO CAPITALIZE IN CLOSING ARGUMENT, WHICH IS FINE, BUT THERE OUGHT TO BE SOME LINKAGE TO SOME AUTHOR OR TO, YOU KNOW, WHAT THE PURPOSE OF IT WAS, WHAT DEPARTMENT IT WAS GENERATED FROM, ET CETERA.

MR. PASAHOW: WE'D BE PLEASED TO STIPULATE WITH DU PONT IF THEY WOULD TELL US THE ANSWER TO THAT QUESTION, WHICH WE'VE BEEN TRYING TO FIND OUT FROM THEM. IF THEY WANT TO TELL US WHAT THIS DOCUMENT -- HOW THE DOCUMENT ORIGINATED OR WHAT GROUP IT ORIGINATED WITH.

THE COURT: HAVE YOU ASKED THOSE QUESTIONS IN DEPOSITION?

MR. PASAHOW: YES.

MR. LEWIS: I ASKED -- THE AUTHENTICATION OF THE CHART CAME FROM A QUESTION I ASKED ONE OF THE LAST DEPOSITIONS IN THE CASE WHERE DOCTOR ANDERSON IDENTIFIED THIS CHART AS HAVING BEEN PREPARED BY A FELLOW NAMED KENNEDY O'BRIAN WHOSE NAME APPEARS ON

THE FRONT OF THE FILE.

WE HAD NOT TAKEN HIS DEPOSITION AND WE DIDN'T HAVE A CHANCE TO FOLLOW-UP ON THAT BEFORE THE TRIAL. BUT PRESUMABLY DU PONT COULD FIND OUT WHAT THE SOURCE IS, WITH THAT LEAD THEN WE'D BE HAPPY TO STIPULATE.

THE COURT: THAT IS SOMETHING THAT SHOULD HAVE REALLY BEEN ACCOMPLISHED AND COMPLETED IN DISCOVERY, UNLESS THEY WERE HIDING THE BALL OR DECLINED TO ANSWER THE QUESTION AT SOME POINT, AS OPPOSED TO JUST NOT HAVING TIME TO FOLLOW IT UP.

MR. KURZ: YOUR HONOR, MIGHT HELP THINGS, WE HAVE NO OBJECTION TO THE CHART WHICH IS ONE OF THE OTHER EXHIBITS, WE WILL WITHDRAW OUR OBJECTION TO THE CHART.

AS FAR AS EVERYTHING EASY WE BELIEVE THAT A WITNESS WAS ASKED ABOUT THIS DOCUMENT AND COULDN'T IDENTIFY IT. THAT'S ONE OF THE PROBLEMS, IT WAS NOT IDENTIFIED, IT WAS NOT AUTHENTICATED AND IT HASN'T BEEN.

THE COURT: I'LL TELL YOU WHAT: BETWEEN NOW AND THE END OF THE WEEK YOU FIND OUT FOR ME WHERE IT CAME FROM. BECAUSE I'M NOT GOING TO LET DU PONT OFF THE HOOK THAT EASILY BY ALL OF A SUDDEN HAVING SOMEBODY SAY, GEE, WE DON'T KNOW WHERE IT CAME FROM, FROM THE BOWELS OF OUR ARCHIVES.

YOU TELL ME WHERE IT CAME FROM THEN I'LL DECIDE WHAT'S GOING TO HAPPEN TO IT.

MR. FIGG: I'M NOT GOING TO GET INVOLVED IN THIS ARGUMENT.

THE COURT: NOW, THERE'S NOT GOING TO BE ANY MORE ARGUMENT. IT'S 1:30 AND, BELIEVE ME, WE HAVE TO HAVE SOME TIME BEFORE THE 2:00 O'CLOCK TRIAL.

WE'LL TAKE UP THE REST OF THIS STUFF AT ANOTHER DATE.

THE CHART COMES IN AND I WANT BY -- IT WON'T BE FRIDAY. TOMORROW'S THURSDAY. BY MONDAY, I WANT TO KNOW WHERE THE REST OF THIS DOCUMENT CAME FROM, AND WHO ITS AUTHOR WAS AND WHEN.

MR. FIGG: WE CAN TELL YOU WHERE IT CAME FROM.

THE COURT: WHO, WHAT, WHERE AND WHEN.

MR. FIGG: IT CAME FROM KENNEDY O'BRIAN. THAT'S WHY HIS NAME IS ON THE FILE. WE PUT THAT ON THERE TO HELP CETUS IDENTIFY WHICH FILE FOLDERS THESE DOCUMENTS CAME FROM, AND WE'VE TOLD CETUS THAT WAS WHAT THAT NAME MEANT ON THERE.

THEY CHOSE NOT TO DEPOSE KENNEDY O'BRIAN. THEY'RE COMPLAINING THEY HAVE NO TESTIMONY ABOUT THE DOCUMENT.

THE COURT: WHO'S KENNEDY O'BRIAN? HE'S A DU PONT EMPLOYEE?

MR. LEWIS: I DON'T KNOW HIS TITLE, YOUR HONOR.

THESE DOCUMENTS, WERE, AS MR. KURZ INDICATED, REFERRED TO IN THE CONTEXT OF AN ANSWER ASKING ABOUT INFRINGEMENT ISSUES. YOUR HONOR BIFURCATED THAT AND WE DIDN'T TAKE INFRINGEMENT DISCOVERY, ABOUT ALL EXCEPT PERHAPS THIS PAGE.

THE COURT: HERE WE ARE, AND YOU MAY WELL BE LEFT WITHOUT THIS DOCUMENT.

OKAY. WE'LL SEE YOU TOMORROW AT 8:00 O'CLOCK.

(COURT ADJOURNED AT 1:31 P.M. TO RECONVENE THURSDAY, FEBRUARY 7, 1991, AT 8:00 A.M.)