A. THAT'S RIGHT.

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

THE COURT: MAY DR. SMITH BE EXCUSED WITHOUT BEING SUBJECT TO BEING RECALLED?

MR. PASAHOW: I HOPE SO, YOUR HONOR, YES.

THE COURT: I'M SURE HE HOPES SO, TOO; RIGHT?

THANK YOU VERY MUCH, DR. SMITH. YOU MAY STEP DOWN.

(WITNESS EXCUSED)

MR. PASAHOW: OUR NEXT WITNESS WILL BE DR. KARY MULLIS.

(PAUSE IN PROCEEDINGS)

THE COURT: YOU WANT TO STAND HERE? I'LL ADMINISTER THE OATH SINCE WE'VE LOST OUR COURT CLERK.

WOULD YOU RAISE YOUR RIGHT HAND.

KARY BANKS MULLIS, DEFENDANT'S WITNESS, SWORN

THE COURT: IF YOU'D HAVE A SEAT HERE. AND GIVE US YOUR NAME, AND ALSO SPELL YOUR NAME FOR US, FIRST AND LAST, I THINK.

THE WITNESS: MY NAME IS KARY BANKS MULLIS, K-A-R-Y, B-A-N-K-S, M-U-L-L-I-S.

THE COURT: THANK YOU.

THE WITNESS: IT'S DR. KARY B. MULLIS.

DIRECT EXAMINATION

BY MR. PASAHOW:

Q. GOOD AFTERNOON, DR. MULLIS.

A. GOOD AFTERNOON, MR. PASAHOW.

Q. MAYBE I SHOULD HELP CLEAR THINGS OFF UP HERE.

A. WE'VE GOT A LOT OF STUFF.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. PASAHOW) DR. MULLIS, DO YOU HAVE EXHIBIT B-1, THE '202 PATENT, THERE?

A. B-1? LET'S SEE. I'VE GOT -- THESE MUST BE THE '195 AND THE '202, YES.

Q. AND YOU ARE THE INVENTOR, KARY MULLIS, ON THE '202 PATENT.

A. THESE ARE MY PATENTS, YES.

Q. COULD YOU PLEASE DESCRIBE FOR US YOUR PERSONAL BACKGROUND.

A. WELL, I -- I START WITH -- I WENT TO COLLEGE, IF THAT'S FAR ENOUGH BACK, OR DO YOU WANT TO GO FURTHER BACK THAN THAT?

Q. THAT'S FINE.

A. I WENT TO GEORGIA TECH AND GOT A DEGREE THERE IN CHEMISTRY.

I STARTED IN CHEMICAL ENGINEERING, AND I REALIZED ABOUT HALFWAY THROUGH THAT ENGINEERING WAS -- WAS FUN, BUT CHEMICAL ENGINEERING WAS NOT GOING TO BE ALL THAT MUCH FUN, AND I LIKED CHEMISTRY A LOT BETTER. AND I ALSO STARTED GETTING INTERESTED IN PHYSICS AND QUANTUM ELECTRODYNAMIC TYPE THINGS.

IT'S -- ALL KIND OF EXCITING STUFF WAS HAPPENING ABOUT THEN IN CHEMISTRY, AND IT . . . I WAS SORT OF OSCILLATING BACK AND FORTH BETWEEN WHAT I WAS GOING TO DO FOR A LIVING.

BUT I ENDED UP WITH A DEGREE IN CHEMISTRY, AND THEN I WENT -- I HAD NOTICED THAT . . . IN READING THINGS, LIKE IN TIME

MAGAZINE, SOME REAL EXCITING THINGS WERE HAPPENING IN CALIFORNIA. THAT WAS ABOUT 1966.

AND I DECIDED TO APPLY TO THE GRADUATE SCHOOL IN BIOCHEMISTRY AT THE UNIVERSITY OF CALIFORNIA IN BERKELEY. AND I -- I FELT LIKE I WAS VERY LUCKY TO GET IN, BECAUSE THEY HADN'T TAKEN ANYBODY FROM GEORGIA TECH, SO I DIDN'T KNOW ANYBODY THERE TO WRITE AND SAY, "HEY, MAKE SURE MY APPLICATION GETS PROCESSED RIGHT." SO IT WAS A BIG CHANGE.

I WENT INTO BIOCHEMISTRY -- INTO THE BIOCHEMISTRY DEPARTMENT, AND I WAS STILL TRYING -- AT THAT POINT, I WAS NOT SURE WHETHER I WANTED TO BE A BIOCHEMIST OR AN ASTROPHYSICIST.

AND I HAD READ A LOT OF ASTROPHYSICS, I'D TAKEN PHYSICS COURSES AT GEORGIA TECH, AND I KNEW YOU PROBABLY COULDN'T MAKE A LIVING BEING AN ASTROPHYSICIST BUT YOU COULD MAKE A LIVING BEING A BIOCHEMIST, SO I WENT TO -- TO THE GRADUATE SCHOOL THERE AND STARTED TAKING BIOCHEMISTRY COURSES.

(PAUSE IN PROCEEDINGS)

THE WITNESS: SHALL I JUST GO RIGHT THROUGH MY -- MY EDUCATION THERE OR --

Q. (BY MR. PASAHOW) WELL, WHY DON'T WE STOP AT U.C. FOR A MOMENT.

WHILE YOU WERE AT THE UNIVERSITY OF CALIFORNIA, DID YOU TEACH?

A. I TAUGHT IN, LIKE -- GRADUATE STUDENTS USUALLY, AFTER A COUPLE YEARS, END UP TEACHING A COUPLE OF COURSES. I LIKED THAT

AND SO -- I MEAN, MOST OF THEM DON'T LIKE IT. IT'S SORT OF LIKE A DUTY YOU HAVE TO PERFORM, AND I REALLY KIND OF LIKED IT.

SO ANY TIME I GOT A CHANCE TO GIVE LECTURES OR TO TEACH, I WOULD DO IT, WHETHER -- AND, IN GENERAL, WHEN I WAS A GRADUATE STUDENT, I DID IT FOR FREE. LATER, AS I -- RIGHT AFTER I LEFT, I GOT MY DEGREE THERE, I SPENT THE SUMMER TEACHING A COURSE AND . . . SO I -- I HAD TAUGHT A LOT BY THE TIME I GOT OUT.

Q. WHEN DID YOU RECEIVE YOUR DOCTORATE DEGREE FROM THE UNIVERSITY OF CALIFORNIA?

A. 1972.

Q. NOW, WE HEARD THAT NATURE MAGAZINE IS ONE OF THE ONE OR TWO PREMIER PUBLICATIONS IN THE ENGLISH LANGUAGE.

ARE YOU FAMILIAR WITH NATURE MAGAZINE?

A. I SUBSCRIBE TO IT, AND I HAVE READ IT FOR YEARS, YEAH. I LIKE IT.

Q. HAVE YOU EVER PUBLISHED AN ARTICLE IN IT?

A. I PUBLISHED MY VERY FIRST ARTICLE IN THAT, AND THAT WAS IN 1968 WHEN I WAS A -- I WAS A SECOND YEAR GRADUATE STUDENT IN BIOCHEMISTRY THERE WORKING IN THE LABORATORY OF J. B. NEILANDS ON SOME BIOCHEMICAL THINGS.

AND I WAS STILL INTERESTED IN ASTROPHYSICS, AND I WAS TAKING ASTROPHYSICS COURSES AT THE UNIVERSITY. AND I ONE DAY GOT AN IDEA THAT I THOUGHT WAS REALLY CLEVER, AND IT WAS A THEORY. IT WAS A DESCRIPTION OF THE UNIVERSE, A THEORY OF THE

UNIVERSE, WHAT'S CALLED A COSMOLOGY.

AND SO I JUST -- I WROTE IT DOWN AND SENT IT TO NATURE. AND IT WAS KIND OF NAIVE FOR A GRADUATE STUDENT IN BIOCHEMISTRY TO BE SENDING A THEORY OF THE UNIVERSE TO NATURE, SO THEY REJECTED IT RIGHT OFF, AND -- BUT I SENT IT BACK. I REVISED IT AND I SENT IT BACK. I PUT IN A FEW MORE FANCY WORDS, AND THEY ACCEPTED IT. AND -- IT SAID THE SAME THING. IT JUST SAID IT IN A LOT FANCIER LANGUAGE THE SECOND TIME. AND IT FIT THEIR FORMAT A LITTLE BETTER, SO . . .

YEAH. THAT WAS MY FIRST EXPERIENCE WITH NATURE.

Q. WHAT DID YOU DO AFTER YOU GRADUATED FROM THE UNIVERSITY OF CALIFORNIA?

A. WELL, I -- I WAS -- I HAD MARRIED THIS WOMAN FROM THE MIDWEST AND -- JUST IN MY FINAL YEAR OF GRADUATE SCHOOL. AND SHE WAS APPLYING TO MEDICAL SCHOOL IN LOTS OF DIFFERENT PLACES, AND THE PLACE THAT SHE GOT IN WAS IN -- BACK IN HER HOME STATE, IN KANSAS, SO . . .

I HAD -- I HAD PLANNED TO DO POST-DOCTORAL WORK ON THE EAST COAST OR ON THE WEST COAST, THINKING THAT SHE'D GET INTO SOME SCHOOL NEAR THE MIDDLE OR EAST COAST OR WEST COAST.

AND I HADN'T PLANNED ON GOING TO KANSAS BECAUSE THERE WAS REALLY NOT A LOT OF EXCITING BIOCHEMISTRY, AS FAR AS I KNEW, GOING ON IN KANSAS. IT TURNED OUT IT WAS NOT SO BARREN AS ALL THAT.

AND I SPENT TWO AND A HALF YEARS THERE WORKING IN THE

PEDIATRIC CARDIOLOGY DEPARTMENT, WHICH IS KIND OF A BIG JUMP FROM BEING AN ORGANIC CHEMIST, BUT THEY NEEDED A -- THERE WAS A COUPLE OF PEDIATRIC CARDIOLOGISTS AND PATHOLOGISTS THERE WHO NEEDED -- OR THEY THOUGHT THEY NEEDED A BIOCHEMIST TO WORK WITH THEM.

SO THEY HAD A PROBLEM WHICH HAD TO DO WITH -- WELL, THEIR RESEARCH INTEREST WAS A DISEASE CALLED IDIOPATHIC RESPIRATORY DISTRESS SYNDROME. IRDS, WE CALLED IT.

IT'S SOMETHING THAT HAPPENS TO KIDS THAT -- THEY'RE -- LIKE PREMATURE BABIES DON'T HAVE THEIR LUNGS COMPLETELY DEVELOPED, AND THEY -- A LOT OF TIMES, PREMIES ARE GOING TO HAVE TO HAVE HEART SURGERY ALSO PRETTY EARLY IN THEIR LIFE, AND WITH AN INSUFFICIENT -- WHEN THEY GO INTO HEART SURGERY, THE -- THEY'RE IMPROPER -- THE LUNGS AREN'T DEVELOPED WELL ENOUGH, EITHER.

AND THE LUNG DOES THIS FUNNY THING, WHICH IS THAT IF THE BLOOD COMING THROUGH IT IS NOT BEING PROPERLY OXYGENATED, THE PART OF THE LUNG THAT'S NOT PROPERLY OXYGENATED IN THE BLOOD SORT OF SHUTS ITSELF DOWN. IF THE WHOLE LUNG IS NOT WORKING RIGHT, THE WHOLE LUNG SHUTS ITSELF DOWN.

IT'S PROBABLY A MECHANISM FOR DEFENDING YOURSELF AGAINST AN INJURY, BUT IN THESE KIDS, THE WHOLE LUNG IS MESSED UP.

SO WHEN THEY GO INTO SURGERY, THE HEART PRESSURES -- THE RIGHT HEART PRESSURE, BECAUSE OF THE FACT THE BLOOD COMING

OUT OF THE RIGHT SIDE OF THE HEART IS SUPPOSED TO GO THROUGH THE LUNG -- IT CAN'T GO THROUGH THE LUNG BECAUSE THE LUNG HAS SQUEEZED ITSELF CLOSED -- THE HEART PRESSURE GOES UP A LOT. A LOT OF KIDS DIE.

SO WE WERE TRYING TO FIGURE OUT IF THERE WAS ANY WAY TO UNDERSTAND THAT MECHANISM BASED ON BIOCHEMISTRY; IN OTHER WORDS, COULD YOU FIGURE OUT WHAT KIND OF BIOCHEMICAL IS BEING RELEASED BY THE PART OF THE LUNG THAT'S THE -- THAT'S SENSING THE FACT THAT IT'S UNDEROXYGENATING THE BLOOD THAT'S CAUSING THAT WHOLE PROCESS. IT'S SOMETHING -- BECAUSE WE COULD FIGURE OUT A WAY TO STOP IT IF WE COULD KNOW WHAT WAS CAUSING IT.

SO WE STUDIED IT FOR, I DON'T KNOW, TWO OR THREE YEARS; PUBLISHED SOME PAPERS. IT TURNS OUT IT'S A VERY, VERY DIFFICULT PROBLEM. WE MADE SOME PROGRESS ON IT, BUT WE CERTAINLY DIDN'T CURE THE SYNDROME.

Q. WHAT WAS YOUR POSITION AT THE UNIVERSITY OF KANSAS?

A. I THINK I WAS BEING PAID AS A TEACHING ASSOCIATE, BUT IT REALLY WAS MORE LIKE A POST-DOCTORAL FELLOWSHIP, EXCEPT FOR THE FACT THAT I WAS THE BIOCHEMIST IN A GROUP OF PEOPLE THAT WEREN'T BIOCHEMISTS.

I WAS LEARNING A LOT OF MEDICINE; THEY WERE LEARNING SOME BIOCHEMISTRY.

IT WASN'T LIKE YOU GO TO A PLACE WHERE SOMEBODY -- I WOULD HAVE PROBABLY ENDED UP. IF IT HADN'T BEEN FOR GAIL SENDING ME TO KANSAS, MARRYING ME, I WOULD HAVE ENDED UP IN A

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LABORATORY OF SOME OTHER BIOCHEMIST WHO WAS FAIRLY MORE EXPERIENCED THAN I.

BUT, THIS WAY, I SORT OF BROADENED MY EDUCATION. I DIDN'T LEARN A LOT OF BIOCHEMISTRY. I LEARNED A LOT ABOUT PHYSIOLOGY AND MEDICINE AND STUFF.

BUT I WOULD HAVE THOUGHT OF IT SORT OF LIKE A POST-DOCTORAL FELLOWSHIP.

Q. WHAT DID YOU DO AFTER YOU LEFT THE UNIVERSITY OF KANSAS?

A. THEN I CAME BACK OUT HERE AND WENT TO -- I GOT A POST-DOCTORAL FELLOWSHIP AT THE UNIVERSITY OF CALIFORNIA AT SAN FRANCISCO, OUT HERE AT THE MED CENTER, AND WORKED IN THE -- IN THE LABORATORY OF THIS MAN NAMED WOLFGANG SADEE (PHONETIC).

AND HE WAS INTERESTED IN THE -- WHAT'S CALLED THE PHARMACOKINETICS OF MORPHINE, BUT -- WHICH MEANS HOW FAST DOES -- DO MORPHINE AND OTHER OPIATE TYPE DRUGS GET IN AND OUT OF YOUR SYSTEM WITH VARIOUS ROUTES OF ADMINISTRATION, THINGS LIKE THAT.

AND THAT FIELD HAD SUDDENLY BECOME REAL EXCITING BECAUSE SOMEONE HAD JUST DISCOVERED THAT THERE WERE INTERNAL OPIATES, THAT THERE WERE THINGS MADE IN YOUR BODY THAT WERE SIMILAR TO OPIUM. THEY HAD SIMILAR EFFECTS TO OPIATES IN THAT THEY MADE YOU FEEL THAT SAME SENSE OF WELL-BEING AND THAT KIND OF THING. AND THAT WAS, IN FACT, WHAT THE WHOLE OPIUM BUSINESS WAS ABOUT.

THAT WAS WHERE MORPHINE WAS GOING WHEN IT MADE YOU FEEL

WONDERFUL WAS TO THESE LITTLE CENTERS THAT WERE THERE FOR THE REASON THAT YOU MADE STUFF LIKE THAT YOURSELF, PARTICULARLY WHEN YOU WERE INJURED OR SOMETHING LIKE THAT, AND YOUR BODY WAS TRYING TO KEEP YOU FROM FREAKING OUT.

SO WE STUDIED THAT, AND THAT WAS REALLY KIND OF FUN, STUDIED THE BINDING OF THOSE ENKEPHALINS AND STUFF TO THOSE RECEPTORS.

Q. DURING WHAT PERIOD DID YOU HAVE THIS FELLOWSHIP AT THE UNIVERSITY OF CALIFORNIA?

A. LET'S SEE, THAT WOULD BE -- I THINK I GOT BACK HERE IN ABOUT 1975, AND SO THAT WOULD HAVE BEEN ABOUT '75, '76, '77. MAYBE IT WAS -- IT WAS PROBABLY LATE '75 UNTIL LATE '77, '78.

I MIGHT HAVE THOSE FIGURES OFF. I HAVE A HARD TIME WITH YEARS. I'VE LATELY LEARNED HOW TO KEEP THEM STRAIGHT BECAUSE OF THIS PATENT THING, BECAUSE EVERYBODY WANTS TO KNOW WHEN DID THIS HAPPEN, WHEN DID THIS HAPPEN.

Q. LET ME SHOW YOU WHAT WE'VE MARKED AS EXHIBIT B-28 AND ASK IF THAT'S A RESUME OF YOUR BACKGROUND.

A. NOW, THIS WILL BE HELPFUL.

OKAY. IT'S '77 TO '79.

THIS IS A RESUME OF MY BACKGROUND, YES.

Q. WHAT DID YOU DO IN 1979?

A. WELL, IN 1979, I HAD DECIDED THAT I WANTED TO GET BACK INTO SOMETHING THAT WAS A LITTLE MORE CHEMICAL THAN I WAS DOING. I WAS WORKING ON CHEMICALS IN ORGAN -- IN, LIKE, RATS, BASICALLY,

AND STUFF LIKE THAT IN THE LAB, AND I REALLY GOT TIRED OF DOING THAT.

AND I ENJOYED ORGANIC CHEMISTRY PROBABLY MORE THAN ANYTHING ELSE I EVER LEARNED, AND SO I -- AND I NOTICED THAT SUDDENLY IT WAS POSSIBLE TO SYNTHESIZE DNA, THAT THEY WERE REALLY STARTING TO, YOU KNOW.

I MEAN, THEY HAD BEEN DOING IT FOR A LONG TIME, A LITTLE BIT, BUT FINALLY -- DNA WAS FINALLY COMING ALIVE AND I DECIDED TO GET INVOLVED IN THAT. IT LOOKED LIKE THAT WAS A REALLY INTERESTING FIELD.

AND SO I -- I KNEW SOME PEOPLE -- OR AT LEAST ONE PERSON REALLY WELL OVER AT CETUS CORPORATION AND, THROUGH HIM, I -- I KNEW THAT THERE WAS A POSITION THERE AVAILABLE FOR AN ORGANIC CHEMIST WHO COULD SYNTHESIZE THESE LITTLE PIECES OF DNA THAT WE'VE BEEN TALKING ABOUT. THEY CALL IT AN OLIGONUCLEOTIDE CHEMIST. OR AN UGLY-OH-NUCLEOTIDE CHEMIST.

BUT THAT WAS -- I WENT OVER THERE AND INTERVIEWED. I GAVE THEM A TALK TO PROVE THAT I COULD MAKE ORGANIC CHEMICALS, AND . . . THEY DECIDED, WELL, ONE ORGANIC CHEMIST IS AS GOOD AS ANY OTHER.

THEY JUST NEEDED AN ORGANIC CHEMIST AND -- ALTHOUGH I HAD NO EXPERIENCE MAKING OLIGONUCLEOTIDES AT THE TIME, BUT I HAD MADE A LOT OF OTHER CHEMICALS. SO THEY HIRED ME, WHICH I THINK IT WAS PROBABLY A DUMB THING TO DO AT THE TIME, BUT I DIDN'T TELL THEM BECAUSE I -- THEY COULD HAVE FOUND AN EXPERIENCED

OLIGONUCLEOTIDE CHEMIST, BUT IT TURNED OUT IT WAS -- THAT IT WORKED OUT ALL RIGHT BECAUSE I QUICKLY LEARNED HOW TO MAKE OLIGONUCLEOTIDES.

AND I DIDN'T COME IN WITH A LOT OF PREJUDICES ABOUT HOW TO MAKE THEM. I JUST WENT TO THE LITERATURE THAT WAS AVAILABLE AND LOOKED AT THE NEWEST METHODS THAT WERE COMING OUT. AND I WAS ALWAYS WATCHING FOR THOSE KIND OF THINGS RATHER THAN SORT OF DEPENDING ON THE OLD-FASHIONED METHODS THAT THEY WERE -- AT THE TIME, THEY HAD A LAB THERE THAT WAS USING METHODS THAT WERE QUITE OUTDATED OR -- YOU KNOW, OUTDATED THEN MEANT TWO OR THREE YEARS OLD.

BUT THEY WERE OUTDATED AND I DIDN'T -- I CAME IN THINKING THEY'D BE DOING BRAND NEW KIND OF METHODS, AND SO THAT WAS PROBABLY TO THEIR ADVANTAGE THAT THEY DIDN'T HIRE AN EXPERIENCED CHEMIST.

Q. BEFORE WE GO INTO THE DETAILS OF YOUR EMPLOYMENT AT CETUS, LET ME ASK:

HAVE YOU EVER DONE A PCR REACTION WITH YOUR OWN HANDS?

A. YES, I DID THE FIRST ONE, AND I'VE DONE PROBABLY HUNDREDS -- THOUSANDS PROBABLY SINCE THEN.

IT'S HARD TO SAY WHAT'S A REACTION. IF YOU COUNT THE NUMBER OF TUBES I'VE USED UP DOING THEM, IT'S PROBABLY IN THE TENS OF THOUSANDS.

Q. ANYWAY, YOU'VE DONE A LOT OF THEM.

A. I'VE DONE A LOT OF THEM. THAT'S SORT OF BEEN A GOOD LIVING

FOR ME.

Q. NOW, AFTER YOU WENT TO WORK AT CETUS, AT SOME POINT, WERE YOU GIVEN YOUR OWN LABORATORY?

A. YEAH. THERE WAS . . . THERE -- I WENT TO WORK THERE FOR THE ORGANIC CHEMIST THAT WAS THERE, AND AFTER I THINK IT WAS ABOUT A YEAR -- IT MAY NOT HAVE BEEN QUITE A YEAR -- WE HAD SOME DIFFERENCES ABOUT HOW WE THOUGHT THINGS OUGHT TO BE, AND I -- THEY FINALLY SEPARATED OFF INTO TWO LABS, SO THAT I HAD MY OWN ORGANIC SYNTHESIS LABORATORY.

Q. HOW SOON AFTER YOU WENT TO CETUS DID YOU SYNTHESIZE YOUR FIRST OLIGONUCLEOTIDE?

A. WELL, I THINK IT TOOK ABOUT -- I THINK IT WAS ABOUT THREE MONTHS, SOMETHING LIKE THAT. IT -- I HAD A -- A PERIOD, SORT OF ABOUT -- THERE'S ABOUT TWO MONTHS IN THERE WHERE I WAS SORT OF JUST FIGURING OUT WHAT WAS GOING ON, LEARNING A FEW THINGS.

THEY BROUGHT SOMEBODY IN WHO WAS AN OLD LONG-TIME -- HE HAD BEEN A -- AN OLIGONUCLEOTIDE CHEMIST FOR A LONG TIME AND HE TRAINED ME A LITTLE BIT.

AND THEN I THINK THERE WAS SORT OF A -- AN EMERGENCY -- WHICH WE HAD A LOT OF EMERGENCIES AT CETUS IN THOSE DAYS -- WHERE THEY SUDDENLY WANTED SOMETHING REALLY BAD, AND THEY THOUGHT THAT THEY SHOULD HAVE HAD IT A MONTH OR TWO AGO, AND I SET OUT TO DO THAT WITH A COUPLE OF TECHNICIANS THAT WERE THERE WORKING WITH ME.

AND WE FINALLY MADE A 15 BASE LONG OLIGONUCLEOTIDE. I

THINK THAT WAS IN THE WINTER THE FIRST YEAR THAT I GOT THERE, WHICH WOULD HAVE BEEN THE WINTER OF 1980.

Q. GOING ON FROM THERE, HOW MANY OF THESE PIECES ABOUT 15 BASE PAIRS LONG DID YOU MAKE, SAY, IN THE FIRST YEAR YOU WERE THERE?

A. IT HAD -- IT HAPPENED PRETTY FAST. AFTER WE -- AFTER WE GOT THE FIRST ONE, AND WE SORT OF FIGURED OUT WHAT WE WERE DOING THEN, AND WE ALSO HAD -- WELL, WE'D JUST GOTTEN MORE AND MORE EXPERIENCE.

I'D SAY WE PROBABLY MADE 10 MORE BEFORE, YOU KNOW, TWO MONTHS WAS GONE, AND THEN PROBABLY 10, 20, OR 30 THE FIRST YEAR, I'D SAY, SOMETHING LIKE THAT. I'D HAVE TO LOOK -- I'VE GOT RECORDS OF THAT SOMEWHERE BACK OVER IN THE BASEMENT AT CETUS PROBABLY.

Q. HOW -- WHEN YOU WOULD MAKE A PARTICULAR SEQUENCE INTO AN OLIGONUCLEOTIDE, HOW MUCH WOULD YOU MAKE?

A. WE ACTUALLY MADE QUITE A BIT. WE WERE DOING THIS IN -- THESE DAYS, IT'S MADE IN LITTLE TEENY QUANTITIES IN MACHINES. BUT WE WERE DEALING WITH BIG FLATS, YOU KNOW, LIKE HUGE QUANTITIES OF SMELLY LIQUIDS, THINGS THAT OTHER PEOPLE THOUGHT WERE SMELLY. I LIKE THE SMELL OF CHEMICALS. BUT LOTS OF BIG QUANTITIES OF THINGS.

AND SO WE -- AND WE WERE ALWAYS BEING VERY CONSERVATIVE, BECAUSE IF YOU DO SOME -- YOU DON'T JUST PUSH A BUTTON. IN FACT, YOU DON'T EVEN PUSH A BUTTON THESE DAYS. I'VE HEARD THAT THESE DAYS FROM PEOPLE WHO DON'T UNDERSTAND WHAT

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THEY'RE TALKING ABOUT, BECAUSE THEY'RE NOT OLIGONUCLEOTIDE CHEMISTS, AND THEY DON'T REALIZE THERE'S A LOT OF HASSLE INVOLVED STILL. IT'S JUST A LOT EASIER.

BUT BACK THEN, IT WAS REALLY A HASSLE AND IT WOULD BE MONTHS YOU WOULD BE SOMETIMES ON ONE PROJECT. SO YOU'D START WITH LARGE AMOUNTS JUST IN CASE SOMETHING HAPPENED DOWN THE ROAD, SO YOU MIGHT SCREW UP, AND ONE OF THE REACTIONS MIGHT BE REALLY BAD INSTEAD OF AVERAGE.

AND SO YOU WANTED TO BE WAY OUT AHEAD BECAUSE THE YIELDS OF THE REACTIONS WOULD ALWAYS -- IF YOU DID -- STARTED UP -- IF YOU GOT A 50 PERCENT YIELD IN THE FIRST ONE AND A 50 PERCENT YIELD IN THE SECOND ONE AND A 50 PERCENT YIELD IN THE THIRD ONE, YOU'RE DOWN TO, YOU KNOW, ABOUT 12 PERCENT. AND THEN IF YOU SUDDENLY GET A 1 PERCENT YIELD INSTEAD OF A 50, YOU'D BETTER HAVE A LOT.

SO WE HAD A LOT MORE THAN WE NEEDED REALLY. BUT THE AMOUNT THAT WE WOULD PROCESS RIGHT TO THE VERY END WOULD BE MAYBE 20 WHAT THEY CALL -- THEY HAVE A UNIT CALLED OD UNIT. I DON'T KNOW IF WE'VE HEARD THAT HERE YET, BUT IT'S ABOUT 30 MICROGRAMS. I KNOW YOU'VE HEARD THAT WORD BUT . . . A MICROGRAM IS LIKE A . . . A GNAT'S EYE OR SOMETHING LIKE THAT.

SO 30 MICROGRAMS IS NOT A LOT, BUT IT'S ONLY NOT A LOT IF YOU'RE PLANNING TO EAT IT. IF YOU'RE GOING TO USE IT IN AN OLIGONUCLEOTIDE EXPERIMENT, 30 MICROGRAMS IS QUITE A LOT, AND I . . . EXCUSE ME. I MIGHT JUST RAMBLE IF YOU . . .

Q. GOING BACK TO THESE OD'S, HOW MANY OF THEM DO YOU THINK YOU WOULD MAKE IN AN INDIVIDUAL SYNTHESIS BACK IN THOSE EARLY DAYS?

A. WELL, THE VERY LEAST THAT WE'D EVER MAKE WOULD BE TWO OR THREE. I MEAN, THAT WOULD BE THE VERY LEAST. AND THAT WOULD BE VERY CONSERVATIVE. WE WOULD PROBABLY END UP MAKING 20 -- 10 OR 20 OD'S IN A PARTICULAR SYNTHESIS.

Q. NOW, IF -- I KNOW YOU DIDN'T HAVE PCR BACK THEN, BUT HOW MANY PCR REACTIONS COULD YOU DO WITH ONE OD OF PRIMER?

A. IF I USE A . . .

I THINK -- SEE, I USED TO DO A PCR REACTION, AND I'D USE ABOUT, WHAT, A HUNDRED PICOMOLES OF PRIMER AND AN OD IS A COUPLE OF NANOMOLES, SO THAT'S . . . 30? 50.

(PAUSE IN PROCEEDINGS)

THE WITNESS: MAYBE A COUPLE HUNDRED. YOU COULD -- YOU KNOW, YOU CAN DO THESE REACTIONS -- I MEAN, THERE'S NO -- YOU DON'T HAVE TO ALWAYS DO IT IN THE SAME VOLUME, AND SO IF YOU WANTED TO DO -- IF YOU WANTED TO DO IT WITH LESS, YOU CERTAINLY COULD.

I COULD -- I KNOW PEOPLE IN THE WORLD WHO DO THEIR PCR REACTIONS IN FIVE MICROLITERS. I DO THEM IN A HUNDRED. BUT YOU CAN DO IT IN FIVE. THAT MEANS YOU CAN USE 20 TIMES LESS.

THERE'S NO REAL STRICT AMOUNT THAT IT TAKES TO DO A PCR REACTION, REALLY, BECAUSE YOU HAVE A LOT OF VARIABLES UNDER YOUR CONTROL WHEN YOU'RE DOING THOSE KIND OF THINGS. I MEAN, WE'VE HEARD THAT HERE ABOUT HOW YOU DON'T HAVE ENOUGH TO DO IT AND IT

TAKES MORE. THAT'S NOT REALLY TRUE, I WOULD SAY.

Q. (BY MR. PASAHOW) LET'S TRY AND STICK TO THE QUESTION.

A. OKAY.

Q. AT SOME POINT, YOU GOT SOME AUTOMATIC MACHINERY AT CETUS?

A. IN ABOUT 1981, I THINK IT WAS, A COMPANY CALLED BIOLOGICALS OF CANADA CAME TO SAN FRANCISCO, THIS BIG INTERNATIONAL MEETING, AND ADVERTISED THAT THEY HAD DEVELOPED A DEVICE THAT WOULD AUTOMATE THE SYNTHESIS OF OLIGONUCLEOTIDES. AND IT WAS A BIG BLACK BOX --

Q. BEFORE YOU --

A. -- AND SO WE BOUGHT ONE.

Q. BEFORE YOU BOUGHT THAT FIRST MACHINE, HAD THE METHOD YOU USED TO MAKE THE OLIGONUCLEOTIDES STAYED THE SAME?

A. NO, NO. WE HAD BEEN MODIFYING IT RAPIDLY AS WE WENT ALONG. AS A MATTER OF FACT, WE WERE ALREADY MAKING THEM A LOT FASTER THAN IN THE VERY BEGINNING.

I HAD DONE A LOT OF SORT OF PIONEERING WORK IN CHANGING THE METHODS. I WAS ALWAYS TRYING TO MAKE IT EASIER BECAUSE WE -- WE ALWAYS HAD A BIG WORKLOAD, AND ANYTHING I COULD DO TO MAKE IT FASTER, MORE EFFICIENT, I DID. AND SO WE HAD -- I MEAN, I'VE DONE LOTS OF LITTLE EXPERIMENTS AND IMPROVED THE METHOD QUITE A BIT.

Q. WHAT IMPROVEMENTS DO YOU RECALL MAKING?

A. WELL, THE THING THAT I DID THAT WAS THE -- SORT OF THE -- ONE OF THE NICEST THINGS I'VE EVER DONE -- AND WHAT SORT OF

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NEVER GOT USED VERY MUCH BECAUSE AUTOMATED MACHINES CAME IN -- WAS I FIGURED OUT A WAY -- WE WOULD BE MAKING THESE THINGS, DOING WHAT THEY CALL BLOCK CONDENSATIONS WHERE YOU'D TAKE TWO HALVES OF THE MOLECULE YOU WERE TRYING -- YOU'D START OUT WITH MONOMERS AND STICK THEM TOGETHER, AND THEN YOU'D TAKE -- YOU'D TAKE DIMERS AND TAKE TWO DIMERS AND STICK THEM TOGETHER, AND ALL OF THIS STUFF WAS BEING DONE IN WHAT WAS CALLED FULLY PROTECTED FORM, MEANING THAT WE WEREN'T EXACTLY USING THE SAME MONOMERS THAT WE WERE TALKING ABOUT HERE. THERE WERE THOSE, PLUS A WHOLE LOT OF ORNAMENTAL ONES, MAKING THEM MANIPULATABLE.

BUT WE WOULD DO -- EVERY TIME WE WOULD DO A CONDENSATION, WE WOULD HAVE TO FIGURE OUT -- WE WOULD HAVE THE PRODUCT, THEN WE'D HAVE ONE OR TWO, BOTH OF THE REACTIONS THAT HADN'T COMPLETELY REACTED. WE'D HAVE ALL KINDS OF SIDE PRODUCTS.

WE HAD TO PUT IT IN SOME KIND OF SYSTEM, AND THE ONE WE USED THE MOST WAS THIN-LAYER PLATE OR THIN-LAYER CHROMATOGRAPHY WHERE YOU JUST HAVE -- IT LOOKS LIKE ABOUT A PIECE OF PAPER, EXCEPT IT'S GOT A LAYER OF SORT OF CRYSTALLINE MATERIAL ON THE SURFACE, SORT OF LIKE VERY FINE SAND THAT STICKS TO IT.

AND YOU PUT THE MATERIAL ON THE BOTTOM OF THAT AND DIP IT INTO A -- JUST LET IT SIT DOWN INTO A LIQUID, LIKE A METHANOL OR SOMETHING, AND THAT WOULD SLOWLY SORT OF DRIFT UP THE PLATE BECAUSE IT WOULD BE WETTING THE DRY SUBSTRATE ON THE SURFACE OF THE PLATE AND SORT OF JUST SUCK IT UP LIKE CAPILLARITY.

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AND AS IT DID THAT, IT WOULD MOVE THE COMPOUNDS UP THE PLATE AT DIFFERENT RATES, DEPENDING ON WHAT THEY WERE, HOW THEY LIKED THE METHANOL, AND HOW THEY LIKED THE PLATE. SEPARATE THINGS.

AND WE WOULD END UP THERE WITH A WHOLE BUNCH OF LITTLE BANDS UP THE PLATE, AND WE COULD TELL THEY WERE THERE BY UV LIGHT SHINING ON THEM, BUT WE COULDN'T TELL WHICH ONE WAS OUR PRODUCT. WE COULD GUESS WHICH ONE WAS OUR PRODUCT BUT WE COULDN'T TELL.

AND THE ONE THAT WAS OUR PRODUCT, WHAT WE WANTED TO DO WAS SCRAPE ALL THAT STUFF OFF THE PLATE, LIKE WITH A RAZOR BLADE, INTO A BEAKER AND LOOPED, MEANING GET THE PRODUCT OFF THAT SILICA GEL -- THE STUFF ON THE PLATE WAS CALLED A SILICA GEL.

SO WE'D HAVE TO SCRAPE THEM ALL OFF A LOT OF TIMES AND PROCESS THEM ALL. THEN WE'D HAVE TO FIGURE OUT WHICH ONE WAS THE RIGHT ONE AND WHICH ONES WERE TO BE THROWN AWAY. AND THAT WOULD TAKE ABOUT TWO DAYS.

WE DIDN'T HAVE TO WORK SOLID FOR TWO DAYS, BUT THE PROCESS -- THERE WERE A LOT OF SLOW STEPS IN THERE THAT TOOK ABOUT TWO DAYS.

AND THEN THE RESULTS WEREN'T ALL THAT GREAT WHEN WE GOT TO THE END. SOMETIMES WE'D KNOW FOR SURE THAT THIS WAS OUR PRODUCT AND SOMETIMES WE WEREN'T.

AND IT'S REALLY SCARY WHEN YOU'RE TRYING TO DO

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SOMETHING THAT TAKES 10 OR 15 STEPS AND YOU'RE NOT EVEN SURE ON THE THIRD STEP WHETHER THE THING YOU'RE PUTTING INTO IT IS THE RIGHT THING.

SO I FIGURED OUT A METHOD. I WAS GETTING INTERESTED IN COMPUTERS, AND I HAD THIS REALLY -- WE HAD A MACHINE THERE CALLED A SPECTROPHOTOMETER, WHICH I THINK THEY MENTIONED THOSE KIND OF THINGS HERE. IT'S A MACHINE THAT MEASURES LIGHT.

AND YOU PUT A LITTLE TEST TUBE IN IT -- A CUVETTE THEY CALL IT -- AND PUT A SOLUTION IN THERE AND SHINE LIGHT THROUGH IT.

AND YOU CAN SHINE DIFFERENT FREQUENCIES, LIKE YOU CAN PUT 260 NANOMETERS, OR 280, AND VARIOUS -- AND YOU CAN MEASURE HOW MUCH OF VARIOUS FREQUENCIES OF LIGHT GET ABSORBED BY WHATEVER'S IN THAT LITTLE CUVETTE.

AND WHAT I DISCOVERED THAT I COULD DO WAS, BY KNOWING THE SEQUENCE THAT I THOUGHT I WAS MAKING, THE THING I WAS HOPING I WAS GOING TO GET, BY KNOWING THAT, AND KNOWING -- AND HAVING A BUNCH OF NUMBERS THAT I HAD CALCULATED FROM SOME OTHER EXPERIMENTS, I COULD CALCULATE WHAT THE RATIOS OF THOSE -- OF THE LIGHT ABSORBENCIES SHOULD BE FOR ANY PARTICULAR THING I WAS GOING TO MAKE.

SO I COULD SAY, IF THIS IS REALLY WHAT I THINK IT IS, AND I PUT THESE NUMBERS THAT I TAKE OFF THE SPECTROPHOTOMETER INTO MY COMPUTER PROGRAM, IT'LL CHEW THROUGH THOSE AWHILE, AND THEN IT'LL SAY, YES, THAT IS RIGHT, OR, NO, GOOD LUCK, YOU KNOW,

GO AWAY.

IT WOULD TELL YOU HOW BAD OFF IT WAS OR HOW CLOSE IT WAS, SO THAT -- IT IMMEDIATELY GAVE US A METHOD TO ANALYZE WHAT WE WERE DOING AND IN A QUANTITATIVE KIND OF WAY. AND IT REALLY IMPROVED THE -- WHAT WE CALLED THE TRIESTER BLOCK CONDENSATION METHOD.

BUT ABOUT THREE MONTHS AFTER I GOT THAT THING REALLY WORKING WELL, WE GOT A MACHINE FINALLY IN THE LAB THAT REALLY WAS -- IT WAS -- IT DID THE SYNTHESIS IN A DIFFERENT WAY.

IT WAS AN AUTOMATED DEVICE AND WE WORKED ON HOW TO GET THAT TO WORK. AND THAT SORT OF -- AFTER THAT, WE DIDN'T NEED MY BEAUTIFUL METHOD, WHICH I -- IS FOR SALE, IF ANYBODY WANTS IT.

Q. GOING TO THIS FIRST MACHINE, YOU SAID IT CAME AROUND 1981 FROM BIOLOGICALS OF CANADA?

A. OKAY. THAT ONE CAME IN, AND WE TRIED TO GET IT TO WORK AND IT WOULD NOT WORK, SO WE SENT IT BACK.

AND THEN A FRIEND OF MINE THAT I HAD MET WHEN I WAS AT UCSF, NAMED RON COOK, HAD STARTED A LITTLE COMPANY OVER IN SAN RAFAEL CALLED BIOSEARCH, AND HE HAD DEVELOPED A MACHINE. AND HE HAD MADE THREE LITTLE PROTOTYPES OF IT.

AND SO HE BROUGHT ONE, KNOWING THAT I WAS WORKING OVER AT CETUS DOING OLIGONUCLEOTIDES. HE BROUGHT ONE OVER THERE. HE KEPT ONE OF THEM, AND HE TOOK ANOTHER ONE TO GENENTECH.

AND THE THREE OF US WORKING TOGETHER SOMEWHAT, BUT ALSO SOMEWHAT INDEPENDENTLY, GOT -- FINALLY FIGURED OUT HOW TO --

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THOSE WERE EASY TO MAKE WORK. IT DIDN'T TAKE A LOT OF WORK TO RUN. IT MADE A GOOD MACHINE.

THE CHEMISTRY WE PLAYED WITH SOME, AND RON PLAYED WITH SOME, AND TWO AT GENENTECH PLAYED WITH DIFFERENT CHEMISTRIES. THOSE MACHINES WORKED WELL.

SUDDENLY, WHAT HAD BEEN TAKING US A LOT OF TIME AND EFFORT TO DO WAS -- IT WAS -- IT WAS NOT TRIVIAL, LIKE IT'S NOT JUST PUSHING A BUTTON. YOU HAVE TO KEEP ALL THE BOTTLES FULL OF ALL THE RIGHT THINGS, AND YOU HAVE TO MAKE ALL THOSE CHEMICALS YOURSELF, OR EITHER YOU HAVE TO KNOW HOW TO QUALITY CONTROL THEM WHEN THEY COME FROM THE MANUFACTURER AND STUFF. BUT IT DID MAKE IT A HECK OF A LOT EASIER.

Q. DID YOU HAVE MORE TIME AS A RESULT OF THIS MACHINE ARRIVING IN YOUR LAB?

A. YEAH, AND -- BUT -- BETWEEN THAT AND THE FACT THAT I HAD REALLY GOTTEN INTERESTED ENOUGH IN THE COMPUTER TO TAKE EVERY TIME-CONSUMING THING THAT I EVER DID THAT WAS REPETITIVE AND PUT IT ON THE COMPUTER.

SO A LOT OF MY ADMINISTRATIVE KIND OF TASKS, THERE WERE THINGS -- I MEAN, I WAS SORT OF DIRECTING THE LAB, AND THERE WERE FOUR OR FIVE PEOPLE IN THE LAB. YEAH, THERE WERE ABOUT FOUR AT THAT POINT.

AND WE WERE MAKING A LOT OF -- MAKING OLIGONUCLEOTIDES IS -- LIKE, AFTER WE GOT IT WORKED OUT, IS JUST A LOT OF ADMINISTRATIVE STUFF, TRYING TO KEEP TRACK OF EVERY SYNTHESIS

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AND HOW IT WAS MADE AND EVERY BATCH OF STUFF. A LOT OF THAT STUFF I MANAGED TO GET ON THE COMPUTER.

AND THEN I DEVELOPED A LOT OF OTHER ANALYTICAL ROUTINES THAT, WHEN THE PEOPLE IN THE LAB WOULD USE THOSE AND THEY WOULD TAKE -- THEY WOULD -- INSTEAD OF HAVING TO CALCULATE THINGS OUT THEMSELVES, THEY WOULD TAKE AND PUT IT IN MY COMPUTER PROGRAMS, AND THE COMPUTER PROGRAMS WOULD KEEP TRACK OF WHAT WAS GOING ON.

IT WOULD MAKE RECORDS OF -- IT'S LIKE SOMEBODY MADE THIS COMPOUND AND PUT IT IN THIS. HERE ARE THE NUMBERS FROM IT. THAT WOULD BE IN A PLACE WHERE I COULD EASILY LOOK AT IT.

SO . . . AND THE WAY -- AND THE COMPUTER PROGRAMS COULD BE SET UP SO THAT THEY WOULD WATCH FOR THINGS THAT WEREN'T WORKING RIGHT, AND THEY WOULD SORT OF SEND UP A FLAG AND THEN I'D HAVE TO BE NOTIFIED.

BUT, BASICALLY, I HAD THE LAB RUNNING ON -- WELL, THE COMPUTER WAS TAKING CARE OF MORE STUFF THAN I WAS AFTER AWHILE, SO I HAD LOTS OF TIME.

THE ANSWER IS YES.

Q. WHAT DID YOU DO WITH THAT TIME?

A. I STARTED -- WELL, YOU KNOW, I LIKE TO PLAY AROUND IN THE LAB, AND SO I HAD ALL THESE OLIGONUCLEOTIDES, AND I REALLY DIDN'T KNOW TOO MUCH ABOUT THE PROPERTIES OF OLIGONUCLEOTIDES BECAUSE NOBODY REALLY, YOU KNOW, HAD TOO MUCH TIME TO PLAY WITH THEM.

WE KNEW SOME OF THE THINGS THEY WOULD DO AND I KNEW

WHAT OTHER PEOPLE HAD DONE WITH THEM IN THE LITERATURE, SO I WENT TO PLAY WITH THEM MYSELF.

I STARTED DESIGNING LITTLE EXPERIMENTS TO DO VARIOUS THINGS WITH THEM. I COULD GIVE YOU SOME EXAMPLES OF ONE OF THEM OR . . . OF MANY.

Q. WELL, THERE'S ONE OF THEM IN WHICH YOU LEARNED SOME INFORMATION ABOUT THE PROCESS OF DENATURATION AND RENATURATION WE'VE BEEN TALKING ABOUT?

A. OH, YEAH. I -- I WASN'T TRYING TO DO -- THAT'S NOT WHAT I WAS TRYING TO FIND OUT, BUT I FOUND THAT OUT.

WHAT I WAS TRYING TO DO WAS FIGURE OUT IF THERE WAS A WAY, KNOWING THE SEQUENCE OF ONE, LIKE IF YOU KNOW THE A, C, G, T PART OF IT, OR WHATEVER SEQUENCE IT IS, IF YOU HAVE -- IF YOU HAVE TWO OLIGONUCLEOTIDES AND YOU -- AND THEY HAVE COMPLEMENTARY SEQUENCES -- YOU'VE HEARD THIS STUFF -- THEY'LL STICK TOGETHER, LIKE TWO LITTLE BAR MAGNETS, KIND OF, YOU CLICK, EXCEPT THEY'RE SQUIGGLIER PROBABLY. BUT WHEN THEY COME TOGETHER, THEY DO MAKE IT KIND OF RIGID.

BUT THE TEMPERATURE -- THEY'LL COME TOGETHER AND THEY'LL STAY TOGETHER IF THE TEMPERATURE IS LOW ENOUGH. IF YOU RAISE THE TEMPERATURE HIGH ENOUGH, THEY'LL SLOWLY SHAKE APART.

AND DIFFERENT SEQUENCES AND DIFFERENT LENGTHS HAVE DIFFERENT TEMPERATURES AT WHICH THEY DO MOST OF THEIR SHAKING APART. LIKE, THEY START SHAKING APART AT, SAY, 55, AND BY THE TIME THEY'RE UP TO 75, THEY'RE REALLY COMING APART, AND THEN 85,

THEY'RE COMPLETELY APART, THAT SORT OF THING.

SO YOU CAN CALCULATE . . . THERE'S A LOT -- THERE WERE A LOT OF FORMULAS AROUND THAT SUPPOSEDLY WOULD HELP YOU CALCULATE THE MELTING TEMPERATURE FOR A GIVEN SEQUENCE IF YOU KNEW THE SEQUENCE. BUT THOSE FORMULAS, NONE OF THEM WERE REALLY CORRECT, BECAUSE IT WAS A REALLY COMPLICATED PROCEDURE.

I MEAN, IT REALLY IS A VERY SEQUENCE-DEPENDENT THING THAT NOBODY COMPLETELY UNDERSTANDS YET.

BUT I DECIDED TO DO SOME EXPERIMENTS WHERE I WOULD JUST MELT OLIGONUCLEOTIDE PAIRS. I'D MAKE TWO THAT WERE COMPLEMENTARY TO EACH OTHER AND PUT THEM INTO A SPECTROPHOTOMETER, AND YOU CAN WATCH THEM MELT IN A SPECTROPHOTOMETER BECAUSE THEY ABSORB MORE LIGHT WHEN THEY'RE SEPARATE THAN THEY DO WHEN THEY'RE STUCK TOGETHER.

BECAUSE WHEN THEY'RE STUCK TOGETHER, THEY SORT OF DON'T PRESENT QUITE AS WIDE A TARGET FOR THE LIGHT. THEY'RE JUST LIKE LITTLE TEENY THINGS WHEN THEY'RE NOT APART. SO THEY ABSORB MORE LIGHT WHEN THEY'RE APART. THAT'S ALL YOU NEED TO KNOW TO UNDERSTAND.

SO I PUT TWO OLIGONUCLEOTIDES IN A CUVETTE AT A TEMPERATURE, LIKE, 30 DEGREES. THEN I'D RAISE THE TEMPERATURE UP TO WHERE I'D -- AND I'D WATCH THE LIGHT GOING THROUGH THE CUVETTE THE WHOLE TIME.

SO I WATCHED FOR THE LIGHT JUST TO DROP OFF. IF I WERE WATCHING THEM -- IF I WAS GOING FROM A HIGH TEMPERATURE TO A LOW

TEMPERATURE, I'D JUST PLOT THE RATE AT WHICH THE -- THE -- THE LIGHT ABSORBENCE DECLINED AS A FUNCTION OF TEMPERATURE. AND THEN, GOING BACK THE OTHER WAY, I'D LET THE LIGHT ABSORBENCE INCREASE.

SO YOU CAN DO THE EXPERIMENT BOTH WAYS. YOU CAN HAVE THE TWO THINGS SITTING IN A SOLUTION AND, YOU KNOW, SEPARATE FROM EACH OTHER. AND YOU CAN DROP THE TEMPERATURE AND THEN THEY'LL FIND EACH OTHER, AND YOU CAN DO IT THAT WAY. THAT'LL HAPPEN AT A PARTICULAR TEMPERATURE.

AND IF YOU DO IT BACKWARDS, WHERE YOU START OFF WITH IT AS A DUPLEX AND THEN YOU HEAT IT, IT'LL EVENTUALLY COME APART. AND THAT'LL HAPPEN -- THAT THING WILL HAPPEN AT THE SAME TEMPERATURE, REALLY, IF YOU DO IT SLOW ENOUGH GOING UP AND DOWN. AND IF YOU --

Q. COULD I GET YOU TO DRAW THAT THING YOU'RE DOING WITH YOUR HANDS?

A. YEAH.

THE COURT: COULD WE GET HIM TO DO THAT TOMORROW?

THE WITNESS: SURE.

MR. PASAHOW: OF COURSE, YOUR HONOR.

THE COURT: IT IS 1:00 O'CLOCK AND, AS YOU MAY OR MAY NOT KNOW, I START ANOTHER TRIAL AT 2:00.

MR. PASAHOW: OH.

THE COURT: AND SO . . . WE NEED TO GET ALL OF THIS STUFF CLEARED UP, AND I KNOW WE'VE GOT SOME OTHER MATTERS TO

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TAKE CARE OF, SO WE'LL PICK IT UP FROM THERE TOMORROW.

THE WITNESS: OKAY.

THE COURT: OKAY. I KNOW YOU'LL BE ON THE STAND A LOT LONGER THAN THIS, ANYWAY. A LOT LONGER.

SO THE JURY IS EXCUSED UNTIL TOMORROW AT 8:00 O'CLOCK. PLEASE FOLLOW THE INSTRUCTIONS YOU'VE BEEN GIVEN.

AND IF YOU COULD PUT YOUR -- WE HAVE ANOTHER JURY IN THERE IN THE AFTERNOON, AND IF YOU COULD PUT YOUR BOOKS ON -- IS THERE ROOM ON THAT FAR SIDE TABLE?

THE JURORS: (NODDING HEADS.)

THE COURT: OKAY. FINE. IF YOU COULD DO THAT, I WOULD APPRECIATE IT.

THANK YOU. YOU'RE EXCUSED. WE'LL SEE YOU TOMORROW. AND YOU MAY STEP DOWN, DR. MULLIS.

THE WITNESS: THANK YOU.

(JURY EXCUSED)

(OPEN COURT, JURY NOT PRESENT:)

THE COURT: OKAY. DID YOU GET A TAB ON A-182, MR. FIGG?

MR. FIGG: WE DON'T HAVE ONE ON THERE YET, YOUR HONOR.

(DISCUSSION HELD OFF THE RECORD)

THE COURT: ARE YOU GOING TO MOVE THAT INTO EVIDENCE?

MR. FIGG: YES.

THE COURT: OKAY. IS THERE ANY OBJECTION TO THAT COMING IN?

MR. PASAHOW: WHICH IS A-182?

THE COURT: DO YOU STILL HAVE -- I THINK IT'S THE ONE STILL UP HERE ON THE STAND.

MR. PASAHOW: OH, NO. NO OBJECTION.

THE COURT: NO OBJECTION. OKAY. THEN A-182 IS ADMITTED.

(PLAINTIFF'S EXHIBIT A-182 RECEIVED IN EVIDENCE)

(PAUSE IN PROCEEDINGS)

THE COURT: AND THEN WHAT ABOUT THE OTHER EXHIBITS THAT WE HAD SOME PROBLEMS ON YESTERDAY?

MR. FIGG: WELL, WE HAD A FEW -- COUPLE OF OTHERS THAT WE MARKED TODAY THAT WE SHOULD MOVE IN. I THINK THE ONLY OTHER ONE WAS A-181.

(PAUSE IN PROCEEDINGS)

MR. FIGG: A-181 IS THE MESSING PAPER AND . . . 182 WE'VE ALREADY TALKED ABOUT.

(PAUSE IN PROCEEDINGS)

MR. FIGG: THE HANDWRITTEN NOTES WERE MARKED FOR IDENTIFICATION. I DON'T KNOW THAT --

THE COURT: AND THAT'S ALL THAT YOU'RE GOING TO DO WITH THEM; RIGHT?

MR. FIGG: THAT'S ALL I PLAN TO DO WITH THEM.

MR. PASAHOW: YOUR HONOR, I WOULD OPPOSE --

THE COURT: YES.

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MR. PASAHOW: -- THE ADMISSION OF EXHIBIT A-181.

THE ARTICLE WAS USED FOR WHATEVER EFFECT IT HAD DURING DR. SMITH'S EXAMINATION. I THINK IT WOULD BE VERY CONFUSING TO ADMIT IT INTO EVIDENCE WHERE SOMEONE COULD START ARGUING THAT IT WAS INTENDED TO HAVE EFFECTS THAT IT DOESN'T.

IT'S VIRTUALLY IMPOSSIBLE TO EVEN TALK ABOUT IMPEACHING DR. SMITH ON THE EXISTENCE OF THIS ARTICLE WITHOUT BEING IN THE PROCESS OF ARGUING THAT IT'S PRIOR ART. AND THAT'S EXACTLY WHAT SHOULDN'T BE ALLOWED, GIVEN THE EXISTENCE OF THE STATUTE AND THE FAILURE TO DESIGNATE IT.

MR. FIGG: YOUR HONOR, THE STATUTE IS DISCRETIONARY WITH THE COURT. ITS -- ITS APPLICATION IS DISCRETIONARY WITH THE COURT.

DR. SMITH TESTIFIED ON DIRECT EXAMINATION AS TO CERTAIN FACTS, AND WE USED THIS ARTICLE TO IMPEACH HIS TESTIMONY. WE FOUND THE ARTICLE AFTER HEARING HIS TESTIMONY AND --

THE COURT: WELL, I --

MR. FIGG: -- SO --

THE COURT: THE PARTS OF THE ARTICLE THAT YOU WISH TO HIGHLIGHT OR POINT OUT BY EXAMINING DR. SMITH ARE REFERRED TO IN THE RECORD AS EITHER A PART OF YOUR QUESTION OR ANSWER.

I DO THINK THAT IT TENDS TO MUDDY THE RECORD BY -- PARTICULARLY SINCE THE JURY WAS TOLD THAT THEY'RE NOT TO CONSIDER IT AS PRIOR ART, AND IT WAS ADMITTED FOR A LIMITED PURPOSE, THAT WHAT HAS COME IN BY WAY OF HIS EXAMINATION IS

IN -- IT'S A PART OF THE RECORD -- BUT THAT THE DOCUMENT ITSELF OR THE PAPER ITSELF SHOULD NOT BE ADMITTED, SO . . . THE PROFFER IS REJECTED.

NOW --

MR. FIGG: THERE WAS ONE OTHER EXHIBIT.

THE COURT: -- ARE THERE OTHERS THAT -- YES.

(PAUSE IN PROCEEDINGS)

MR. FIGG: OH, THIS WAS JUST ONE THAT WE DID NOT -- WE NEGLECTED TO MOVE IN WITH DR. VAN DE SANDE. IT'S EXHIBIT A-179.

MR. PASAHOW: IS THIS THE CORRECTED VERSION?

MR. FIGG: CORRECTED VERSION.

MR. PASAHOW: NO OBJECTION, YOUR HONOR.

THE COURT: 179?

MR. FIGG: A-179.

THE COURT: ADMITTED.

(PLAINTIFF'S EXHIBIT A-179 RECEIVED IN EVIDENCE)

MR. PASAHOW: JUST TO CLARIFY WHAT WE MEAN BY THE CORRECTED VERSION, THERE WAS NO SUBSTITUTION OF ONE NUMBER FOR ANOTHER.

MR. FIGG: NO. WE DIDN'T MOVE THE OTHER ONE IN. RIGHT.

THE COURT: OKAY. HAVE WE GOT THE OTHER EXHIBITS STRAIGHTENED OUT NOW, OR WHERE DO WE STAND ON THIS?

MR. PASAHOW: WELL, I USED ALL THE EXHIBITS DURING DR.

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SMITH'S EXAM THAT I'D LIKE TO MOVE IN.

THEY'RE EXHIBITS B-46, HIS CV.

MR. FIGG: NO OBJECTION

(DEFENDANT'S EXHIBIT B-46 RECEIVED IN EVIDENCE)

MR. PASAHOW: AND THEN EXHIBIT B-160, WHICH IS THE EXCERPT OF CLAIM 1 OR, I SHOULD SAY, THE POSTER.

MR. FIGG: NO OBJECTION.

(DEFENDANT'S EXHIBIT B-160 RECEIVED IN EVIDENCE)

MR. PASAHOW: B-172, WHICH IS THE POSTER OF KLEPPE.

MR. FIGG: NO OBJECTION.

(DEFENDANT'S EXHIBIT B-172 RECEIVED IN EVIDENCE)

MR. PASAHOW: B-173, WHICH IS THE POSTER OF PANET.

MR. FIGG: NO OBJECTION

(DEFENDANT'S EXHIBIT B-173 RECEIVED IN EVIDENCE)

MR. PASAHOW: B-174, WHICH IS THE POSTER FROM THE NATIONAL SCIENCE FOUNDATION GRANT.

MR. FIGG: NO OBJECTION.

(DEFENDANT'S EXHIBIT B-174 RECEIVED IN EVIDENCE)

MR. PASAHOW: B-244, WHICH IS A POSTER OF PAGE 6 FROM THAT SAME GRANT PROPOSAL.

MR. FIGG: NO OBJECTION.

(DEFENDANT'S EXHIBIT B-244 RECEIVED IN EVIDENCE)

MR. PASAHOW: B-30, WHICH IS THE TIMELINE WE USED.

MR. FIGG: NO OBJECTION.

(DEFENDANT'S EXHIBIT B-30 RECEIVED IN EVIDENCE)

MR. PASAHOW: B-181A AND B, WHICH ARE THE TWO PAGES FROM THE SECOND EDITION OF THE CLONING MANUAL.

MR. FIGG: NO OBJECTION TO THAT.

(DEFENDANT'S EXHIBITS B-181A & B-181B RECEIVED IN EVIDENCE)

MR. PASAHOW: AND B-165, WHICH IS THE POSTER OF CLAIM 1 OF THE '195 PATENT.

MR. FIGG: NO OBJECTION.

(DEFENDANT'S EXHIBIT B-165 RECEIVED IN EVIDENCE)

MR. PASAHOW: AND THEN THERE, IN ADDITION, WERE A SERIES OF EXHIBITS THAT I USED DURING DR. VAN DE SANDE'S CROSS-EXAMINATION THAT I READ INTO THE RECORD ONCE AND MR. FIGG WAS TO SEE IF HE HAD ANY OBJECTION TO THEM, AND I'VE NEVER BEEN ADVISED THAT HE DOES.

(PAUSE IN PROCEEDINGS)

MR. FIGG: WE HAD NO OBJECTIONS TO MOST OF THEM. WE CAN GET TO THE SPECIFIC NUMBERS.

SEVERAL OF THESE EXHIBITS, AT LEAST CLOSE TO HALF OF THEM, WERE COPIES OF PAGES FROM THE KLEPPE NOTEBOOKS, AND WE WOULD NOT OBJECT TO THEIR BEING ADMITTED SUBJECT TO ADMISSION OF THE ENTIRE DOCUMENT UNDER RULE 106.

MR. PASAHOW: WELL, MR. FIGG HAS A GOOD POINT, AND I WOULD WITHDRAW MY MOTION AS TO THE NOTEBOOK PAGES.

MR. FIGG: WELL, THEN --

THE COURT: THEREBY LEAVING HIM WITHOUT GETTING THE WHOLE 106 (SIC) IN? IS THAT WHAT YOU'RE SAYING?

MR. PASAHOW: WELL, THE NOTEBOOK PAGES ARE SUBJECT TO YOUR HONOR'S RULING AND INSTRUCTION TO THE JURY, AND OBVIOUSLY IT WOULD BE QUITE CONFUSING TO START FIDDLING WITH THAT, AND THAT HADN'T BEEN OUR INTENT. WE HAD JUST MADE THESE POSTERS SO THE JURY WOULD BE ABLE TO SEE WHAT WE WERE TALKING ABOUT --

THE COURT: OKAY.

MR. PASAHOW: -- AS WE TALKED ABOUT IT.

THE COURT: SO WHERE DOES THAT LEAVE US AS FAR AS 106 (SIC) IN ITS ENTIRETY? OR --

MR. FIGG: IT WASN'T EXHIBIT 106. IT WAS RULE 106. THE -- I FORGET WHAT THE EXHIBIT IS FOR THE NOTEBOOKS.

THE COURT: OH, THE ONE . . .

MR. FIGG: THERE WERE A WHOLE SERIES OF EXHIBITS THAT WERE VARIOUS PORTIONS OF DR. KLEPPE'S NOTEBOOKS.

THE COURT: YOU MEAN 1,006? WHAT ARE YOU . . .

MR. PASAHOW: NO. I THINK I -- WE HAD BETTER TALK

ABOUT THIS OFF THE RECORD, AND WE WILL COME BACK TO YOUR HONOR.

THE COURT: OKAY.

MR. PASAHOW: IT SOUNDS LIKE WE HAVE AGREEMENT, AND WE JUST NEED TO GET THE RIGHT NUMBERS ATTACHED TO IT.

THE COURT: OKAY. OKAY. WHAT ABOUT THE REST OF THE EXHIBITS USED WITH DR. VAN DE SANDE?

MR. FIGG: I THINK THAT'S WHAT MR. PASAHOW INDICATED WE'RE GOING TO HAVE TO GET THE NUMBERS STRAIGHT.

THE COURT: OKAY, ON THOSE.

MR. FIGG: WE'LL HAVE NO TROUBLE DOING THAT.

THE COURT: AND SO THEN YOU'LL TAKE CARE OF THOSE AT ANOTHER TIME.

MR. PASAHOW: YES, YOUR HONOR.

THE COURT: NOW, YESTERDAY, THERE WERE SOME OTHER EXHIBITS THAT YOU WERE GOING TO SORT OUT. HAVE YOU DONE THAT, OR ARE THESE THE ONES YOU'RE TALKING ABOUT?

MR. LEWIS: YOUR HONOR, WE HAVE NOT TALKED ABOUT THE EXHIBITS WE WERE GOING TO SORT OUT YESTERDAY, AND I SUGGEST WE PROBABLY OUGHT TO BEFORE WE BURDEN YOU WITH MORE ARGUMENT ABOUT THEM.

THE COURT: YEAH, BECAUSE IF YOU'RE GOING TO BE ABLE --

MR. FIGG: THAT'S FINE WITH ME.

THE COURT: -- STIPULATE TO SOME OF THEM, THEN THERE'S NO POINT IN -- THERE'S NO POINT IN HASHING THOSE OUT NOW.

OKAY. THEN, FOR THE RECORD, A-182 AND B-46, 160, 172,

173, 174, 244, 30, 181A AND B, AND 165 ARE ADMITTED, AND THE REST WE WILL TAKE UP AT SOME OTHER TIME, I GUESS.

AND WE WILL CONTINUE TOMORROW WITH DR. MULLIS.

WOULD I BE CORRECT IN GUESSING THAT DR. MULLIS WILL BE ON THE STAND ALL OF TOMORROW, OR DO YOU THINK . . .

MR. PASAHOW: I DON'T KNOW HOW MUCH CROSS-EXAMINATION MR. FIGG HAS IN MIND. HIS DIRECT EXAMINATION WILL PROBABLY GO ANOTHER HOUR AND A HALF.

MR. FIGG: I'M A LITTLE CONFUSED. WE WERE INFORMED LAST NIGHT THAT DR. MULLIS' TESTIMONY WOULD BE INTERRUPTED BY DOCTOR -- OR BY MR. ANDERSON.

MR. PASAHOW: WELL, MR. ANDERSON HAS FIXED HIS SCHEDULE, SO THAT'S NOT A PROBLEM NOW. I'M SORRY.

MR. FIGG: OKAY.

THE COURT: OKAY. DO YOU KNOW HOW LONG YOU'LL BE ON CROSS? IT'S A HARD ONE TO GUESS.

MR. FIGG: AFTER I FAILED ON MY ESTIMATE TODAY, I'M RELUCTANT TO GIVE YOU AN ESTIMATE, YOUR HONOR.

THE COURT: OKAY. AFTER DR. MULLIS, WHOM ARE YOU CALLING?

MR. PASAHOW: THEN WE'LL HAVE MR. RUDY ANDERSON.

THE COURT: OKAY. IT WILL HELP A GREAT DEAL IF YOU JUST ANSWER THE QUESTIONS TOMORROW.

THE WITNESS: OKAY. I'LL TRY.

THE COURT: OKAY. THAT WILL GET US THERE A LOT MORE

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QUICKLY.

YES?

MR. FIGG: THERE WAS ONE POINT I NOTICED I -- DURING DR. MULLIS' TESTIMONY, AND ABOUT WHAT HE WAS GETTING READY TO DRAW ON THE PAGE.

I THINK THAT HE'S TALKING ABOUT EXPERIMENTS THAT WERE DESCRIBED IN LABORATORY NOTEBOOKS THAT CETUS REFUSED TO PRODUCE TO US BECAUSE THEY WERE, ACCORDING TO CETUS' DETERMINATION, IRRELEVANT BECAUSE THEY WERE TOO EARLY. IF THAT IS SO, I WOULD OBJECT TO THE TESTIMONY ABOUT THOSE EXPERIMENTS COMING IN.

MR. PASAHOW: IT'S MY UNDERSTANDING, YOUR HONOR, THAT THESE EXPERIMENTS WERE NOT RECORDED IN ANY OF DR. MULLIS' NOTEBOOKS.

MR. FIGG: WELL, OR . . . WE RECEIVED -- THEY IMPOSED A CUTOFF DATE AND WE RECEIVED NO --

THE COURT: DID THESE COME UP IN A DEPOSITION?

MR. FIGG: NO.

(PAUSE IN PROCEEDINGS)

MR. FIGG: WE -- CETUS IMPOSED A CUTOFF DATE AND BASICALLY DOCUMENTS PRIOR TO JULY OF -- OR SEPTEMBER OF 1983 EMANATING FROM DR. MULLIS WERE NOT PRODUCED TO US.

AND, FOR EXAMPLE, WE STARTED IN ONE NOTEBOOK ABOUT HALFWAY INTO THE NOTEBOOK BECAUSE CETUS' CONTENTION IS THAT'S WHERE THE WORK STARTS THAT'S RELEVANT TO PCR.

AND IF DR. MULLIS -- I DON'T THINK DR. MULLIS SHOULD BE

PERMITTED TO TALK ABOUT EXPERIMENTAL WORK THAT HE'D DONE -- THAT HE DID PRIOR TO THAT TIME.

THE COURT: WELL, WHAT IS THE RELEVANCY OF THIS EXPERIMENTAL WORK?

MR. PASAHOW: WHEN HE WAS DOING THIS EXPERIMENT, HE MADE A -- AN OBSERVATION WHICH LATER PROVED TO BE USEFUL TO HIM AS HE WAS CONCEIVING THE CONDITIONS FOR PCR.

THE WORK THAT HE -- THESE EXPERIMENTS THAT HE DID -- AND HE'S PREPARED TO, AND I PLAN TO ELICIT TESTIMONY ABOUT THEM -- WERE INFORMAL EXPERIMENTS THAT WERE NOT RECORDED IN WRITING. THEY WERE JUST -- AS HE PUT IT, HE WAS PLAYING WITH THESE OLIGONUCLEOTIDES IN THE LABORATORY. AND SO NO DOCUMENTS WERE WITHHELD THAT ARE RELEVANT TO THESE EXPERIMENTS.

THE COURT: WELL --

MR. FIGG: WELL, I WOULD LIKE TO REVIEW -- AND I WILL REVIEW HIS DEPOSITION TRANSCRIPT, BECAUSE I THINK WE ASKED HIM TO IDENTIFY HIS WORK THAT HE THOUGHT WAS RELEVANT TO PCR, AND WE STARTED WITH THE FIRST EXPERIMENTS IN SEPTEMBER OF 1983, BUT I'LL REVIEW THAT.

THE COURT: WELL, YOU MAY DO THAT. BE PREPARED TO SHOW ME THOSE TOMORROW --

MR. FIGG: YES.

THE COURT: -- MORNING IF THERE'S STILL GOING TO BE AN OBJECTION.

BUT I THINK WHAT WE MAYBE OUGHT TO DO IS SEE WHAT THAT