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COPY

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

BEFORE THE HONORABLE MARILYN HALL PATEL, JUDGE

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

SAN FRANCISCO, CALIFORNIA
WEDNESDAY, FEBRUARY 13, 1991

APPEARANCES:

FOR PLAINTIFF:

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BART G. NEWLAND, ESQ.

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

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

(APPEARANCES CONTINUED ON NEXT PAGE)

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BY: PETER D. STAPLE, ESQ.

I N D E X

WEDNESDAY, FEBRUARY 13, 1991 8:12 A.M.

(OPEN COURT, JURY PRESENT:)

THE COURT: GOOD MORNING, LADIES AND GENTLEMEN.

THE JURORS: GOOD MORNING.

THE COURT: GOOD MORNING, COUNSEL.

MR. FIGG: GOOD MORNING, YOUR HONOR.

MR. PASAHOW: GOOD MORNING, YOUR HONOR.

MR. LEWIS: GOOD MORNING, YOUR HONOR.

THE COURT: ARE WE READY TO COMMENCE WITH OUR NEXT WITNESS?

MR. LEWIS: IF I MIGHT CLEAN UP ONE ITEM OF BUSINESS:

MR. FIGG HAS TOLD ME HE HAS NO FURTHER CROSS-EXAMINATION OF DR. DAHLBERG, AND THAT BEING SO, I'D LIKE TO MOVE INTO EVIDENCE THE EXHIBITS, HIS TABLES AND CHARTS.

THEY'RE EXHIBITS B-263, 264, 265, 267, 268, AND 269.

MR. FIGG: NO OBJECTION, YOUR HONOR.

THE COURT: THEY ARE ADMITTED, THEN.

MR. LEWIS: THANK YOU.

THE COURT: THANK YOU.

(DEFENDANT'S EXHIBITS B-263, B-264, B-265, B-266, B-267, B-268 & B-269 RECEIVED IN EVIDENCE)

MR. PASAHOW: YOUR HONOR, OUR NEXT WITNESS IS DR. FRENCH ANDERSON.

THE COURT: YES.

THE CLERK: PLEASE RAISE YOUR RIGHT HAND.

W. FRENCH ANDERSON, DEFENDANT'S WITNESS, SWORN

THE CLERK: PLEASE TAKE THE STAND.

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

THE WITNESS: YES. DR. W. FRENCH ANDERSON, SPELLED A-N-D-E-R-S-O-N.

THE COURT: YOU MAY PROCEED.

MR. PASAHOW: THANK YOU, YOUR HONOR.

DIRECT EXAMINATION

BY MR. PASAHOW:

Q. DR. ANDERSON, YOU'RE A MEDICAL DOCTOR?

A. YES.

Q. AND YOU WORK AT THE UNITED STATES GOVERNMENT'S NATIONAL INSTITUTES OF HEALTH; IS THAT CORRECT?

A. YES, THAT IS CORRECT.

Q. WHAT DO YOU DO THERE?

A. I AM A BRANCH CHIEF, WHICH MEANS I RUN A LABORATORY AND I AM AN ADMITTING PHYSICIAN ON THE CLINICAL SERVICE.

Q. WHAT TYPE OF LABORATORY DO YOU RUN?

A. THE NAME OF IT IS THE MOLECULAR HEMATOLOGY BRANCH. IT WAS CREATED BASICALLY TO STUDY AND ATTEMPT TO DEVELOP TREATMENTS FOR GENETIC DISEASES, AND SPECIFICALLY DISEASES OF THE BLOOD. THAT'S THE REASON IT'S CALLED HEMATOLOGY.

Q. IS ~~ADA DEFICIENCY~~ ONE OF THOSE DISEASES?

A. ADA DEFICIENCY IS ONE OF THE DISEASES WE ARE ATTEMPTING NOW TO TREAT, YES.

Q. WHAT IS ADA DEFICIENCY?

A. ADA DEFICIENCY IS A GENETIC DISEASE. IT IS A DISEASE WHERE THE CHILDREN ARE BORN WITHOUT A NORMAL IMMUNE SYSTEM. WHAT THAT MEANS IS THAT THESE CHILDREN ARE SEVERELY AFFECTED BY THE SAME KINDS OF COLDS AND LITTLE INFECTIONS THAT YOUR CHILD OR MY CHILD MIGHT HAVE SOME SNIFFLES OR . . . OR A LITTLE COLD. SUCH LITTLE INFECTIONS CAN KILL THESE CHILDREN.

MOST OF THE SEVERELY INFECTED DIE IN THE FIRST YEAR OF LIFE; MOST OTHERS BY THE SECOND YEAR OF LIFE. THOSE THAT AREN'T AS SEVERELY AFFECTED CAN SURVIVE UNTIL PERHAPS THEIR EARLY TEENS.

BUT THEY ARE VERY AFFECTED. THEY HAVE A FAILURE TO THRIVE; THEY HAVE MANY INFECTIONS; THEY'RE IN THE HOSPITAL. THEY GET INJECTIONS ALL THE TIME. NEEDLES FOR THESE KIDS IS -- IS PART OF THEIR WAY OF LIFE.

Q. HOW IS ADA DEFICIENCY TRADITIONALLY TREATED?

A. THE ONLY SUCCESSFUL TREATMENT HAS BEEN A MATCH BONE MARROW TRANSPLANTATION, WHERE A -- BONE MARROW IS TAKEN FROM A -- A MATCHED DONOR, A BROTHER OR SISTER, AND THEN GIVEN TO -- GIVEN TO THE CHILD, AND THIS -- THIS CAN BE CURATIVE.

ABOUT 30 -- ONLY ABOUT 30 PERCENT OF CHILDREN HAVE A MATCHED DONOR. THE REST OF THEM THERE REALLY IS NO GOOD

TREATMENT.

ONE OF THE THINGS THAT CAN BE DONE IS TO KEEP THEM IN A STERILE ENVIRONMENT. MANY OF YOU MIGHT REMEMBER DAVID THE BUBBLE BOY IN HOUSTON WHO LIVED IN A STERILE BUBBLE FOR THE 11 YEARS OF HIS LIFE. THAT REALLY ISN'T DONE BECAUSE OF ENORMOUS PSYCHOLOGICAL STRESSES THAT THAT PUTS ON THE CHILD.

BUT ONE CAN DO VARIOUS THINGS: GIVE IMMUNOGLOBULIN INJECTIONS; CAN GIVE A DRUG LIKE PEG '88 (PHONETIC), WHICH IS A WEEKLY INJECTION AND A VERY, VERY PAINFUL INJECTION. AND THESE CERTAINLY ARE VERY HELPFUL FOR -- FOR SOME OF THE CHILDREN, BUT BASICALLY WITHOUT A BONE MARROW TRANSPLANTATION, THESE CHILDREN ARE ALWAYS AT RISK FOR SUDDEN LETHAL INFECTION.

Q. NOW, I UNDERSTAND YOU'RE WORKING ON A NEW TREATMENT FOR DISEASES SUCH AS ADA DEFICIENCY.

A. YES. I HAVE . . . BEGAN REALLY 22 YEARS AGO, AND FINALLY JUST THIS LAST YEAR HAVE FINALLY BEEN ABLE TO DEVELOP A THERAPY CALLED GENE THERAPY.

I DON'T KNOW HOW MANY OF YOU MIGHT HAVE HEARD ABOUT IT, BUT . . . WE ALL HAVE GENES, AND IF A GENE IS DEFECTIVE, IT CAN PRODUCE A DISEASE. THERE ARE MANY COMMON ONES. SICKLE CELL ANEMIA IS A GENETIC DISEASE; BETA-THALASSEMIA -- IN FACT, THESE WERE THE DISEASES I CREATED THE HEMATOLOGY SERVICE OF THE HEART INSTITUTE BACK IN 1968 TO -- TO TREAT -- CYSTIC FIBROSIS; TAY-SACHS; DIABETES; VARIOUS KINDS OF MENTAL DISEASES AND SO ON.

WHAT THESE ARE CAUSED BY IS -- IS A . . . A DEFECT IN

THE GENE. AND YOU'VE SEEN HERE THE BASIS OF DNA AND THE A'S AND T'S. A SINGLE BASE BEING DEFECTIVE IN A GENE CAN PRODUCE SICKLE CELL ANEMIA, CAN PRODUCE HEMOPHILIA, OR CAN PRODUCE ADA DEFICIENCY.

AND SO WHAT WE HAVE DEVELOPED OVER THE LAST 20 YEARS IS A PROCEDURE WHERE WE CAN TAKE A NORMAL GENE, IN THIS CASE AN ADA GENE, PUT IT INTO THE CELLS OF THE PATIENT, GIVE THE -- TAKE THE -- TAKE THE BLOOD CELLS FROM THE PATIENT, PUT THE GENE INTO THE BLOOD CELLS, AND PUT THOSE CORRECTED CELLS BACK INTO THE PATIENT.

AND THAT WAS DONE FOR THE FIRST TIME SEPTEMBER 14TH, 1990, AT THE NIH, IN A LITTLE FOUR-YEAR-OLD GIRL.

Q. COULD I GET YOU TO DESCRIBE YOUR EDUCATIONAL BACKGROUND.

A. I WAS -- GOT MY UNDERGRADUATE DEGREE AT HARVARD COLLEGE, WHERE I WORKED WITH PAUL DOTY ON THE STRUCTURE OF DNA, AND ON GENE TRANSFER AND GENE EXPRESSION IN BACTERIA. THAT WAS -- I GUESS I GRADUATED IN 1958.

I THEN SPENT TWO YEARS WITH -- WITH FRANCES CRICK AT THE MRC LABORATORY AT THE CAMBRIDGE, ENGLAND.

Q. THAT'S FRANCIS CRICK WHO WORKED WITH DR. WATSON?

A. YES. YES, THIS IS THE CRICK OF WATSON AND CRICK.

THEN I RETURNED TO HARVARD MEDICAL SCHOOL WITH ADVANCE STANDING, GOT MY M.D. DEGREE IN '63, AND AT THE SAME TIME WORKED IN -- IN PAUL DOTY'S LABORATORY IN THE AREA OF DNA HYBRIDIZATION; TOOK AN INTERNSHIP IN PEDIATRIC MEDICINE AT

BOSTON CHILDREN'S HOSPITAL, WHERE I PERSONALLY CONCENTRATED IN BLOOD DISEASES OF CHILDREN; AND THEN SPENT ONE YEAR AS A POST-DOC AT HARVARD MEDICAL SCHOOL; AND THEN JOINED MARSHALL NIRENBERG AT THE NATIONAL INSTITUTES OF HEALTH TO HELP WITH THE FINAL DECIPHERMENT OF THE GENETIC CODE.

Q. NOW, YOU MENTIONED YOU WERE DOING HYBRIDIZATION WORK WITH DR. DOTY AT HARVARD DURING YOUR TIME IN MEDICAL SCHOOL.

WHAT KINDS OF THINGS WERE YOU DOING?

A. THE . . . THE WHOLE CONCEPT OF DNA BEING A DOUBLE STRAND AND IT COMING APART AND COMING BACK TOGETHER, THAT PHENOMENON, NOT THE -- THE STRUCTURE OF DNA WAS DISCOVERED BY WATSON AND CRICK IN '53, BUT THIS COMING APART AND COMING BACK TOGETHER, THE REALIZATION THAT THAT HAPPENS WITH DNA WAS DISCOVERED IN PAUL DOTY'S LABORATORY IN '59 AND '60.

I HAD BEEN IN DOTY'S LABORATORY AS A STUDENT UP TO '58, SPENT TWO YEARS WITH CRICK GETTING A -- A MASTER'S DEGREE AT CAMBRIDGE, AND THEN CAME BACK TO DOTY. SO THAT DISCOVERY WAS MADE WHILE I WAS IN ENGLAND.

BUT AS SOON AS I CAME BACK, I JOINED IN -- AS A STUDENT NOW, I JOINED IN IN THOSE EARLY STUDIES, UNDERSTANDING THE -- THE PHYSICAL CHEMISTRY OF DNA HYBRIDIZATION AND RNA HYBRIDIZATION, SECONDARY, TERTIARY STRUCTURE, ALL OF THE VARIOUS -- THE THERMODYNAMICS, THE STATISTICAL ANALYSIS OF WHAT HAPPENS WITH MOLECULES, ALL OF THAT INITIAL THEORETICAL WORK THAT PROVIDED A BASIS FOR THE UNDERSTANDING OF DNA

HYBRIDIZATION. FOR -- FOR EXAMPLE, THAT A G-C PAIR IS STRONGER THAN AN A-T.

THAT WAS ALL EARLY WORK DONE IN '60, '61, '62, '63. AND LET ME SAY, I WAS A STUDENT AT THE TIME. I WAS LEARNING. I WAS NOT MAKING -- MAKING THE CONTRIBUTIONS TO THAT.

Q. NOW, YOU THEN WENT ON AND DID A POST-DOCTORAL FELLOWSHIP WITH DR. NIRENBERG?

A. YES. THAT WAS MY SECOND -- SECOND POST-DOC WAS AT THE . . . THE FIRST ONE WAS AT HARVARD MEDICAL SCHOOL. I THEN JOINED MARSHALL NIRENBERG AT NIH IN 1965, YES.

Q. AND YOU SAY YOU WERE WORKING ON DECIPHERING THE GENETIC CODE.

A. YES.

Q. WHAT DID THAT WORK CONSIST OF?

A. THE GENETIC CODE IS BASICALLY THE . . . THE ALPHABET THAT OUR CELLS USE. THE ENGLISH LANGUAGE, AS YOU KNOW, HAS 26 LETTERS. A COMPUTER HAS TWO: PLUS/MINUS, ON/OFF. AND IN THAT ARRAY OF PLUS/MINUS, MINUS/PLUS, YOU CAN GET A GREAT DEAL OF INFORMATION.

DNA IS ALSO A LINEAR SEQUENCE, BUT IT HAS FOUR LETTERS, A, T, G AND C. AND THOSE FOUR LOWERS CAN BE COMBINED THREE AT A TIME INTO CODE WORDS, AND EACH OF THOSE CODE WORDS CARRIES THE INFORMATION FOR ONE OF THE BUILDING BLOCKS OF A PROTEIN, CALLED AN AMINO ACID.

SO IF YOU HAVE FOUR THINGS TAKEN THREE AT A TIME, YOU

END UP WITH 64, AND OF THOSE 64 CODE WORDS, 61 OF THEM REPRESENT AN AMINO ACID, A BUILDING BLOCK. THE OTHER THREE ARE -- ARE -- ARE CONTROL WORDS: START, STOP.

Q. AND WHAT WAS YOUR ROLE IN CONNECTION WITH THIS?

A. OH, MY ROLE IN CONNECTION WITH THIS, I JOINED THE -- THE NIRENBERG LAB AFTER ABOUT 90 PERCENT OF THE ASSIGNMENTS HAD TAKEN PLACE, BUT THOSE LAST -- THOSE LAST FEW WERE REAL PROBLEMS, AND SO I PARTICIPATED VERY ACTIVELY IN -- IN MAKING THE OLIGONUCLEOTIDES THAT WERE INVOLVED IN THE FINAL, FINAL CHARACTERIZATION AND HELPED WITH THE -- THE FINAL ASSIGNMENTS.

THEN, IN RETURN FOR THAT, I WAS HONORED BY DR. NIRENBERG TO MAKE THE FIRST PUBLIC PRESENTATION OF THE FINAL GENETIC CODE, AND THAT WAS AT THE FEDERATION MEETINGS IN ABOUT APRIL OF 1966, WHERE THE -- THE FIRST TIME THAT -- AT A PUBLIC SCIENTIFIC MEETING THE FINAL CODE, AND I WAS HONORED TO BE ABLE TO DO THAT.

Q. COULD YOU GIVE US NOW AN ABBREVIATED SUMMARY OF YOUR WORK AT THE NIH FROM THE TIME YOU WERE IN DR. NIRENBERG'S LAB.

A. YOU WANT ME TO TRY TO SUMMARIZE MY WHOLE CAREER IN THREE OR FOUR MINUTES?

Q. NOT YOUR WHOLE CAREER, BUT THE HIGHLIGHTS PERHAPS.

A. OKAY. ALL RIGHT.

(PAUSE IN PROCEEDINGS)

THE WITNESS: IN WORKING WITH DR. NIRENBERG, AND HAVING . . . FINISHED DECIPHERING THE CODE -- AND THIS WAS SOMETHING

THAT DR. NIRENBERG AND DR. KHORANA, WORKING SEPARATELY, BOTH WON THE NOBEL PRIZE FOR SEVERAL YEARS LATER -- MY FEELING WAS THAT THE TIME WAS RIGHT TO TRY TO APPLY ALL OF THIS BASIC MOLECULAR BIOLOGY KNOWLEDGE TO THE STUDY OF HUMAN DISEASE, AND SPECIFICALLY GENETIC DISEASE, AND INITIALLY BETA-THALASSEMIA AND SICKLE CELL ANEMIA.

SO I WAS GIVEN MY OWN INDEPENDENT LAB, AND AT THE SAME TIME, I CREATED THE HEMATOLOGY SERVICE OF WHAT WAS THEN THE NATIONAL HEART INSTITUTE, NOW THE NATIONAL HEART, LUNG AND BLOOD INSTITUTE, BY BRINGING IN TWO PATIENTS WITH -- WITH BETA-THALASSEMIA, AND THEN WE GRADUALLY BUILT IT INTO A LARGE SERVICE WITH . . . FOR SICKLE CELL AND FOR BETA-THALASSEMIA.

MY FEELING WAS -- AND THAT LAB WAS CREATED TO DEVELOP THE TECHNOLOGY FOR DOING GENE THERAPY. THAT WAS 1968. SO I HAD A VERY DIRECTED LAB FOR 22, 23 YEARS.

AS I'M SURE YOU KNOW, THAT THE WAY THE GENETIC INFORMATION GOES IS DNA TO RNA, PROTEIN. AND FOR HEMOGLOBIN, A SICKLE CELL, FOR EXAMPLE, THERE'S A DEFECT IN THE SIXTH CODE WORD. THAT THEORETICALLY SHOULD BE A DEFECT IN THE RNA AND THEN IN THE FINAL PROTEIN.

VERY LITTLE WAS KNOWN IN 1967, '68, ABOUT ANY OF THOSE MECHANISMS IN MAMMALIAN CELLS OR HUMAN CELLS. A CERTAIN AMOUNT WAS KNOWN IN BACTERIA, BUT THERE WAS VERY LITTLE KNOWN IN ANIMAL CELLS. AND SO I WENT TO WORK TO TRY TO -- TO DISCOVER THE MECHANISMS THAT ARE USED IN ANIMAL CELLS.

AND THE FIRST THING WAS TO TRY TO UNDERSTAND HOW A PROTEIN IS MADE, THE MACHINERY OF THE CELL. HOW DO YOU MAKE THAT PROTEIN? YOU'VE GOT THIS NICE NUCLEIC ACID STRAIN. HOW DO YOU MAKE THE PROTEIN?

AND I WAS VERY FORTUNATE IN BEING ABLE TO DISCOVER THE FACTORS, CALLED INITIATION FACTORS, THE PROTEINS -- THAT ARE REQUIRED FOR MAKING THE PROTEIN.

AND IT TURNED OUT, BY LUCK, THAT THOSE SAME FACTORS THAT WE DISCOVERED THAT MAKES HEMOGLOBIN MAKES EVERY OTHER PROTEIN, AND NOT ONLY DOES IT MAKE EVERY OTHER PROTEIN IN MAMMALIAN CELLS, RELATED FACTORS MAKE EVERY PROTEIN IN EVERY ANIMAL SYSTEM, AND INCLUDING INVERTEBRATES AND PLANTS.

SO IT WAS A VERY MAJOR FINDING, AND IT REALLY CATAPULTED MY LAB TO A -- A MAJOR LABORATORY FAIRLY EARLY.

HAVING THEN LEARNED HOW A MAMMALIAN CELL AND A HUMAN CELL MAKES A PROTEIN, THE NEXT STEP WAS TO DETERMINE IF THE PUTATIVE -- IT HADN'T BEEN DISCOVERED YET; IT HAD BEEN THEORIZED, HADN'T BEEN DISCOVERED YET -- THE MESSENGER OF DNA CARRIED THAT GENETIC DEFECT INFORMATION. NOWADAYS, WE TAKE THAT FOR GRANTED, BUT IN 1969, 1970, YOU WOULDN'T KNOW THAT.

AND WHAT WE WERE ABLE TO DO WAS TO TAKE THE MESSENGER RNA FROM THE BLOOD CELLS OF OUR PATIENT WITH SICKLE CELL ANEMIA AND COOLEY'S ANEMIA, PUT IT IN A TEST TUBE ALONG WITH THESE INITIATION FACTORS FROM A RABBIT, AND SHOW WE COULD MAKE HUMAN SICKLE CELL HEMOGLOBIN AND HUMAN BETA-THALASSEMIA HEMOGLOBIN IN

A TEST TUBE.

IT WAS A . . . IT WAS FELT TO BE A MAJOR FINDING. THIS WAS PRESENTED AT THE PLENARY SESSION OF THE MAJOR CLINICAL MEETINGS, AND IT REALLY ESTABLISHED MY LABORATORY. IT THEN BECAME A VERY LARGE LABORATORY WITH SIGNIFICANT RESOURCES.

WE THEN MOVED -- THOSE DNA/RNA PROTEIN. SO WE HAD UNLOCKED THE RNA PROTEIN AND THEN WENT BACK TO THE DNA TO TRY TO LEARN HOW THE RNA IS MADE.

AND THAT WAS A LOT STICKIER WICKET. THAT -- THAT WAS TOUGH. WE RAN INTO SEVERAL DEAD-ENDS.

BUT THEN SOMETHING HAPPENED THAT WAS VERY SIGNIFICANT, THAT REALLY CHANGED THE WHOLE -- WHOLE DIRECTION OF WHAT I DID, AND THAT IS THE DISCOVERY OF ~~RECOMBINANT DNA~~.

AND IT BECAME CLEAR THEN THAT WE WOULD USE GENES IN GENE THERAPY NOT FROM THE PROCEDURE THAT DR. KHORANA WAS DEVELOPING -- BECAUSE HE WAS THE WORLD'S LEADER AT THAT POINT IN MAKING A GENE -- BUT IT WOULD BE DONE BY RECOMBINANT DNA TECHNOLOGY.

SO I GAVE THE BULK OF MY LAB AWAY AND CREATED A NEW LAB -- I KEPT THE SAME NAME BUT CREATED A NEW LAB -- WENT BACK TO SCHOOL, ESSENTIALLY, LEARNED RECOMBINANT DNA TECHNOLOGY, LEARNED TISSUE CULTURE, AND BEGAN IN 1975 VERY SPECIFICALLY DEVELOPING GENE TRANSFER, GENE EXPRESSION, GENE DELIVERY SYSTEMS TO TRY TO -- TO SPECIFICALLY START THE PROCESS FOR BEING ABLE TO DO GENE THERAPY.

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THE FIRST SYSTEMS I WORKED WITH WERE PUTTING NUCLEIC ACID SEQUENCES INTO RED CELLS, INTO LIPOSOMES AND VARIOUS PARTICLES, AND THOSE DIDN'T WORK TOO WELL.

BUT THEN I HAD THE IDEA THAT MAYBE YOU COULD DO IT BY MAKING A LITTLE TINY HYPODERMIC NEEDLE AND ACTUALLY MICROINJECTING IT INTO THE NUCLEUS OF A CELL.

AND I KNEW OF . . . DR. ELAINE DIACOUMACOS -- D-I-A-C-O-U-M-A-C-O-S, I THINK -- WHO HAS NOW DIED, BUT WAS WORKING UP AT THE ROCKEFELLER UNIVERSITY AND WAS MICROINJECTING PROTEINS. SO I ESTABLISHED A VERY FRIENDLY, FRUITFUL COLLABORATION WITH ELAINE. I DUPLICATED HER EQUIPMENT AND BUILT IT IN MY OWN LAB.

NOW, THE PEOPLE IN MY LAB THOUGHT IT WAS SUCH A HAIRBRAINED IDEA, I COULDN'T EVEN PUT IT IN MY LAB, SO I HAD TO PUT IT ON MY DESK IN MY OFFICE. SO I HAD THIS MICROINJECTION APPARATUS -- IT WAS VERY CRUDE -- WITH ALL THE VARIOUS PARTS TO IT.

IT TOOK A COUPLE OF YEARS TO DO, BUT DEVELOPED THE TECHNIQUE FOR BEING ABLE TO INJECT A SINGLE GENE INTO A CELL AND, IN 1979, REPORTED FOR THE FIRST TIME OF CORRECTING A CELL THAT HAD A GENETIC DEFECT BY INSERTING A SINGLE COPY OF A GENE.

AND THAT WAS -- THAT REALLY ESTABLISHED THE CONCEPT OF GENE THERAPY. FOR THE FIRST TIME, PEOPLE BEGAN TO BELIEVE THAT MAYBE GENE THERAPY WAS GOING TO HAPPEN SOMETIME IN THE NEXT TEN, 20, 30 YEARS.

NOW, OF COURSE, OTHERS -- OTHER WORKERS HAD PUT DNA ON CALCIUM PHOSPHATE, IN OTHER WAYS, AND PUT MANY COPIES, BUT THIS WAS THE FIRST TIME A SINGLE COPY HAD BEEN DONE.

NOW, I ACTUALLY GAVE UP THAT PROCEDURE, WHICH WAS CONSIDERED -- CONSIDERED TO BE A RATHER STRANGE THING TO DO AT THE TIME, BUT IT BECAME VERY SUCCESSFUL. IT'S USED ALL AROUND THE WORLD NOW TO USE THIS TRANSGENETIC MICE, TO PUT GENES INTO OSITES (PHONETIC).

BUT I GAVE IT UP. THE REASON I GAVE IT UP WAS, MY WHOLE GOAL WAS TO DO GENE THERAPY FOR BLOOD DISEASES. IF YOU TWO A BILLION CELLS, AND IT TAKES YOU 30 SECONDS TO GO IN ONE CELL, IT'S NOT GOING TO BE A PROCEDURE YOU CAN USE CLINICALLY. YOU CAN'T GO INTO A BILLION CELLS TAKING A HALF A MINUTE A CELL.

SO I STARTED TRYING TO FIND A DIFFERENT PROCEDURE AND CAME TO THE CONCLUSION ABOUT '89 THAT PERHAPS RETROVIRUSES COULD BE USED.

BY '85, WE HAD CORRECTED THE BLOOD CELLS OF A PATIENT WITH ADA DEFICIENCY -- IN THE TEST TUBE, NOT IN A PATIENT -- BY PUTTING THE ADA GENE INTO A RETROVIRUS AND PUTTING THAT INTO THE PATIENT'S IMMUNE CELLS IN THE TEST TUBE.

IN 1987, WE FIRST SUBMITTED MATERIAL LEADING TO A REQUEST FOR DOING A GENE THERAPY EXPERIMENT. WE WERE INITIALLY NOT SO MUCH TURNED DOWN AS TABLED.

IN 1988, WE REQUESTED AND RECEIVED PERMISSION IN '89 TO PUT A RECOMBINANT MARKER GENE INTO CANCER PATIENTS. WE WENT

INTO THE FIRST PATIENT MAY 22ND, 19 -- 1989, IN A SUCCESSFUL STUDY WHERE WE SHOWED THAT WE COULD DO THE GENE TRANSFER PROCESS IN HUMANS.

WE REQUESTED EARLY IN 1990 PERMISSION TO DO GENE THERAPY ON CHILDREN WITH ADA DEFICIENCY. WE RECEIVED APPROVAL IN EARLY FALL -- IN -- IN MID-SUMMER, AND WENT INTO OUR FIRST PATIENT SEPTEMBER 14TH, 1990, A FOUR-YEAR-OLD GIRL WITH ADA DEFICIENCY.

THAT HAS GONE WELL AND WE HAVE NOW GONE INTO OUR SECOND PATIENT, AND WE WENT INTO TWO CANCER PATIENTS WITH A GENE THERAPY PROTOCOL FOR CANCER . . . ABOUT -- ALL -- ALL IN THE LAST MONTH.

SO THAT'S . . .

Q. (BY MR. PASAHOW) THAT'S THE --

A. A RATHER LENGTHY SUMMARY.

Q. HAVE YOU SERVED AS AN EXPERT CONSULTANT BEFORE?

A. OH, YES. I WAS . . . AN EXPERT AT CONGRESSIONAL HEARINGS ON HUMAN GENETIC ENGINEERING, AT PRESIDENTIAL COMMISSION HEARINGS ON HUMAN GENETIC ENGINEERING, OFFICE OF TECHNOLOGY TRANSFER ASSESSMENT . . . MEETINGS, HEARINGS.

I'M A CONSULTANT FOR VARIOUS HOSPITALS AND UNIVERSITIES ON GENE THERAPY.

I'VE PRESENTED MANY TIMES BEFORE THE RECOMBINANT DNA ADVISORY COMMITTEE ON GENE THERAPY, BEFORE THE HUMAN GENE THERAPY SUBCOMMITTEE, TO THE FOOD & DRUG ADMINISTRATION,

ADVISORY COMMITTEE MEETINGS AND SO ON, YES, SIR.

Q. AND I UNDERSTAND YOU ARE THE FOUNDER AND EDITOR OF A JOURNAL ON HUMAN GENE THERAPY?

A. YES. I'VE BEEN ON THE EDITORIAL BOARD OF A NUMBER OF JOURNALS, BUT WE ESTABLISHED OUR -- A JOURNAL IN OUR OWN FIELD A LITTLE OVER A YEAR AGO, AND I'M THE FOUNDING EDITOR.

Q. LET ME SHOW YOU WHAT WE'VE MARKED AS EXHIBIT B-280.

IS THAT A COPY OF YOUR CV?

A. YES.

Q. AND THAT LISTS ABOUT 250 OR SO PUBLICATIONS. THOSE ARE PUBLICATIONS YOU'VE HAD OVER THE YEARS --

A. YES.

Q. -- IN TECHNICAL JOURNALS?

A. YES.

Q. ARE YOU BEING COMPENSATED FOR YOUR TIME AS AN EXPERT CONSULTANT OR WITNESS IN THIS CASE?

A. YES AND NO. BY THAT, I MEAN, YES, I'M COMPENSATED AT THE RATE OF $250 AN HOUR. HOWEVER, I AM A GOVERNMENT CIVIL SERVANT, AND I HAVE A CAP ON HOW MUCH TIME I CAN SPEND, AND I USED UP MY CAP IN PREPARATION, SO BASICALLY MY TESTIMONY IS FOR FREE.

Q. AT ONE POINT IN THE 1960'S, YOU INDICATED YOU WERE WORKING ON THIS GENETIC CODE RESEARCH AT THE SAME TIME AS RELATED RESEARCH WAS GOING ON IN THE LABORATORY OF DR. KHORANA?

A. YES.

Q. DURING THAT PERIOD, DID YOU START REVIEWING PUBLICATIONS

FROM THE KHORANA LABORATORY?

A. READING THEM, YES. YES, I READ EVERY PAPER OUT OF DR. KHORANA'S LABORATORY FROM THE MID-'60'S UNTIL THE MID-'70'S, AS SOON AS -- AS SOON AS THEY CAME OUT.

ORIGINALLY, BECAUSE WE WERE COMPETING IN THE CODE, BUT THEN AS I MOVED INTO THE PROTEIN SYNTHESIS AREA, IN MY INDEPENDENT LAB, DR. KHORANA MOVED INTO ATTEMPTING AND SUCCESSFULLY SYNTHESIZING A GENE.

NOW, IF YOU'RE GOING TO DO GENE THERAPY, THE FIRST THING YOU NEED IS A GENE, AND THEN A DELIVERY SYSTEM, AND THEN, THIRD, A DETECTION SYSTEM. AND SINCE THE WORLD LEADER IN MAKING A GENE WAS KHORANA, I READ EVERY PAPER AS IT CAME OUT, YES.

Q. DID YOU BECOME AWARE FROM THE PAPERS YOU WERE READING FROM THE KHORANA LABORATORY THAT HE WAS TRYING A TWO-PRIMER SYSTEM FOR COPYING DNA?

A. YES.

Q. NOW, YOU INDICATED YOU HAD WORKED WITH DR. DOTY IN THE EARLY 1960'S WITH DNA HYBRIDIZATION.

DID YOU CONTINUE TO STAY INTERESTED IN THAT FIELD?

A. YES. I'D BEEN . . . NUCLEIC ACID HYBRIDIZATION, DNA HYBRIDIZATION, IS AN AREA THAT HAS BEEN CENTRAL TO WHAT I'VE DONE FOR -- FOR 20 YEARS.

AGAIN, AS WAS SAID, IF YOU'RE GOING TO DO GENE THERAPY, YOU NEED A GENE, YOU NEED TO BE ABLE TO TRANSFER THE GENE, AND YOU HAVE TO BE ABLE TO DETECT THE GENE.

AND IT -- IT HAS BEEN KNOWN SINCE -- SINCE -- WELL, FOR MANY YEARS THAT THE MOST SENSITIVE WAY, SPECIFIC WAY OF DETECTING THE GENE IS BY NUCLEIC ACID HYBRIDIZATION.

SO I WAS INVOLVED AS A STUDENT IN THOSE INITIAL DISCOVERIES AND STUDIES AND HAVE BEEN ACTIVE SINCE AND, DURING THE EARLY '70'S, PUBLISHED A NUMBER OF THE PAPERS THAT ESTABLISHED HOW TO USE HYBRIDIZATION TO DETECT THE AMOUNT OF GLOBIN MEASURED IN DNA, AND HOW TO DETECT ALPHA RATIOS OF GLOBIN, PRACTICAL PAPERS AS WELL AS THEORETICAL PAPERS GOING INTO THE ACTUAL PHYSICAL CHEMISTRY OF HOW THESE REACTIONS WORK.

Q. DOES PCR HAVE ANY RELATIONSHIP TO THE WORK YOU'VE BEEN DOING ON GENE THERAPY?

A. YES. PCR IS THE CENTRAL METHOD THAT WE USE TO DETECT THE GENES IN BOTH THE PATIENT CELLS AS WELL AS IN ANIMAL CELLS IN OUR PRECLINICAL STUDIES.

Q. WHEN DID YOU FIRST BEGIN TO KEEP CLOSE TABS ON THE LITERATURE HAVING TO DO WITH THE SYSTEMS FOR DETECTING THE PRESENCE OR ABSENCE OF DNA SEQUENCES IN CELLS?

A. 1957. 1957, WAS WHEN I WAS A JUNIOR -- SENIOR -- SENIOR AT HARVARD COLLEGE AND WAS DOING FOR THE FIRST TIME A GENE TRANSFER EXPERIMENT. THAT WAS IN BACTERIA BECAUSE NOTHING WAS CONCEIVABLE IN MAMMALS AT THAT POINT.

BUT THAT WAS TRANSFERRING A BACTERIAL GENE FROM ONE BACTERIAL SPECIES TO ANOTHER, AND ALL WE HAD TO LOOK AT AT THAT POINT WAS A CHANGE IN THE CHARACTERISTICS OF THE BACTERIA.

BUT, IN ADDITION, I ATTEMPTED TO WORK OUT, WITH -- WITH SOME SUCCESS, HOW TO BE ABLE TO DETECT CHANGES BASED ON LOOKING AT THE PHYSICAL CHEMISTRY OR THE PROPERTIES, THE PHYSICAL PROPERTIES OF A DNA MOLECULE.

Q. WHEN DID --

A. AND I FOLLOWED THAT FIELD EVER SINCE.

Q. AS YOU FOLLOWED THE FIELD, WHEN DID YOU FIND THAT AN EFFECTIVE DETECTION SYSTEM THAT COULD BE USED FOR GENE THERAPY TYPE OF DETECTION FIRST BECAME AVAILABLE?

A. WOULD YOU REPEAT THAT?

Q. WELL, LET ME TRY TO --

A. NO. I WAS JUST --

Q. -- SIMPLIFY IT.

AND THE QUESTION IS: WHEN DID AN EFFECTIVE DETECTION SYSTEM THAT YOU COULD USE FOR YOUR GENE THERAPY WORK FIRST BECOME AVAILABLE?

A. WELL, THERE ARE VARIOUS KINDS OF GENE DETECTION SYSTEMS, BUT -- BUT THE FIRST TIME THAT ONE WHICH WAS -- WAS EFFICIENT AND PRACTICAL AND COULD BE USED WAS -- THE FIRST TIME I BECAME AWARE OF IT WAS END OF DECEMBER OR FIRST OF JANUARY OF -- DECEMBER OF '85, FIRST OF JANUARY '86, WHEN THE SAIKI SCIENCE PAPER CAME OUT.

Q. NOW, BEFORE THAT TIME, WERE YOU AWARE OF A TECHNIQUE THAT'S BEEN CALLED SOUTHERN BLOTTING?

A. OH, CERTAINLY.

Q. OR SOUTHERN BLOTS, I GUESS IT IS.

A. BOTH. BOTH. BLOTTING IS THE VERB.

Q. CAN SOUTHERN BLOTS WITHOUT PCR BE USED FOR THE KIND OF DETECTION YOU NEED IN HUMAN GENE THERAPY?

A. NO. WE USE SOUTHERN BLOTS AND HAVE USED SOUTHERN BLOTS FOR YEARS. IN FACT, THE GENE TRANSFER TECHNOLOGY -- THE GENE TRANSFER BY MICROINJECTION THAT WE DID IN '79, THAT -- THAT USED SOUTHERN BLOTS, AND WE USED SOUTHERN BLOTS AS PART OF OUR HUMAN GENE THERAPY DETECTION SYSTEM.

BUT SOUTHERN BLOTS WILL ONLY DETECT ABOUT ONE CELL IN TEN WHICH CARRIES A GENE. AT BEST, ONE IN 20. AND WE NEED TO BE ABLE TO DETECT ONE IN A THOUSAND, ONE IN 10,000, ONE IN A HUNDRED THOUSAND. SO ONLY PCR -- AND WE DO IT IN CONJUNCTION WITH SOUTHERN BLOTS. REALLY, FOR US, ONLY PCR IS -- IS USEFUL.

Q. SO YOU DO AN AMPLIFICATION WITH PCR FIRST AND THEN DO SOUTHERN BLOTS --

A. YES.

Q. -- TO DETECT?

A. YES. YOU CAN SEE WITHIN THE BROMIDE BEFORE SOUTHERN BLOT, BUT, FOR OUR PURPOSES, WE REALLY WANT TO NOT ONLY FIND IT BUT QUANTITATE IT.

ARE WE GETTING IT IN ONE IN A HUNDRED THOUSAND CELLS, OR IS IT ONE IN 10,000 CELLS, OR IS IT ONE IN 1,000 CELLS?

SO WE NEED -- WE NEED EVERYTHING WE CAN GET, AND SO WE USE PCR WITH SOUTHERN BLOTTING AS THE MOST SENSITIVE AND MOST

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QUANTITATIVE WAY OF DETECTION.

Q. NOW, WE'VE HEARD THAT THERE ARE OTHER WAYS THAT BIOCHEMISTS OR MOLECULAR BIOLOGISTS HAVE USED TO AMPLIFY DNA BEFORE THEY TRIED TO DETECT AND, IN PARTICULAR, RECOMBINANT CLONING TECHNIQUES.

A. RIGHT.

Q. COULD THOSE BE USED IN THE PLACE OF PCR IN YOUR WORK?

A. OH, NOT IN PLACE OF. WE USE -- I THINK PROBABLY EVERY TECHNIQUE THAT IS USED, WE USE IN ONE WAY OR ANOTHER IN OUR LABORATORY. BUT NONE OF THE OTHERS CAN BE USED AS A DETECTION PROCEDURE FOR IDENTIFYING THE RARE CELL IN A WHOLE ANIMAL OR A WHOLE -- OR A WHOLE PATIENT, OR IN A -- IN A COMPLEX MIXTURE.

Q. NOW, YOU'VE ALREADY REFERRED TO THE DECEMBER 1985 ARTICLE IN SCIENCE THAT WAS AUTHORED BY MR. SAIKI AND HIS CETUS COLLEAGUES, AND THAT'S WHAT WE'VE MARKED AS EXHIBIT B-38?

A. UH-HUH. UH-HUH. YES.

Q. WHEN YOU FIRST READ THAT ARTICLE, WHAT WAS YOUR REACTION TO IT?

A. I DIDN'T BELIEVE IT.

Q. WHAT DIDN'T YOU BELIEVE?

A. I DID NOT BELIEVE THE -- THE CONCLUSIONS OF THE AUTHORS. I BELIEVED THAT THEY DID THE EXPERIMENTS, AND THAT THEY DID IT THE WAY THEY SAID THEY DID IT, AND THEY GOT THE NUMBERS THEY SAID THEY GOT, BUT I DID NOT BELIEVE THEIR CONCLUSIONS.

Q. WHY NOT?

A. WELL, YOU SEE . . . MOLECULAR BIOLOGY ISN'T LIKE MUCH OTHER PARTS OF SCIENCE. YOU CAN'T SEE MOLECULES. EVERYTHING YOU DO IS BASED ON ASSUMPTIONS.

IF YOU WANT TO SEE -- IF YOU WANT TO DO AN EXPERIMENT AND YOU WANT TO KNOW HOW MANY EGGS A CHICKEN LAYS, EVERY MORNING YOU CAN GO IN AND YOU CAN COUNT THE EGGS. AND ONE DAY, IT'S ONE; ANOTHER DAY, IT'S THREE; ANOTHER DAY, IT'S TWO. AND AT THE END OF A PERIOD OF TIME, YOU CAN SAY THIS CHICKEN LAYS 2.3 EGGS A DAY. AND YOU CAN SEE THE CHICKEN AND YOU CAN SEE THE EGGS.

YOU CAN'T SEE MOLECULES, SO EVERYTHING IS BASED ON ASSUMPTIONS.

LET ME -- COULD I HAVE A -- LET ME -- LET ME -- LET ME EXPLAIN, A TEACHING PRACTICE WHICH I DO WITH MY OWN STUDENTS, AND MAYBE IT'LL POINT THIS OUT. AND I'VE DONE THIS FOR YEARS.

A STUDENT WILL COME IN -- BY "STUDENT," I MEAN A GRADUATE STUDENT OR A POST-DOC -- AND SAY, "OH, I'VE GOT SOME -- I'VE GOT SOME EXCITING RESULTS HERE. I'VE BEEN ABLE TO MAKE 20 PICOMOLES OF HEMOGLOBIN."

AND MY RESPONSE WILL BE, "HOW DO YOU KNOW THAT YOU MADE 20 PICOMOLES OF HEMOGLOBIN?"

AND THEY'LL SAY, "OH, LOOK, I'VE GOT THE DATA RIGHT HERE."

AND I WILL SAY, "WHAT YOU HAVE RIGHT THERE ARE NUMBERS ON A PIECE OF PAPER. ALL -- THAT'S ALL YOU KNOW."

ALL YOU KNOW IS, IS THAT YOU TOOK A CLEAR DROP OF

SOLUTION FROM ONE TUBE WHICH WAS -- YOU HAD MADE SOMETHING, YOU THOUGHT IT WAS A TEMPLATE -- AND A CLEAR DROP FROM ANOTHER TUBE THAT WAS LABELED SOMETHING ELSE, AND SEVERAL OTHER TUBES THAT YOU BOUGHT FROM COMPANIES THAT HAD LABELS LIKE AMINO ACID OR LABELS LIKE A NUCLEOTIDE, AND THEN YOU TOOK A BOTTLE AND IT WAS LABELED SODIUM CHLORIDE, AND SO YOU ASSUMED THERE WAS SODIUM CHLORIDE IN THERE, THEN A TUBE THAT SAYS MAGNESIUM AND YOU ASSUMED THERE WAS MAGNESIUM.

YOU PUT ALL THOSE IN A TUBE. YOU PUT THE TUBE IN A WATER BATH. YOU HEATED IT; YOU TOOK IT OUT. MAYBE YOU PUT IT IN A FILTER, RAN A GEL, PUT IT ON A COLUMN. YOU DID A FEW OTHER THINGS, AND THEN YOU PUT IT INTO A MACHINE, AND SOME LIGHTS WENT AROUND AND A PIECE OF PAPER CAME OUT AND IT HAD PRINTED NUMBERS. THAT'S ALL YOU KNOW. EVERYTHING ELSE IS AN ASSUMPTION.

SO ONCE I'VE DONE THAT WITH A STUDENT, THEN THEY'RE MUCH MORE CAREFUL ABOUT -- ABOUT -- ABOUT WHAT THEY SAY, BECAUSE EVERYTHING WE DO IN MOLECULAR BIOLOGY IS BASED ON ASSUMPTIONS.

SO WHEN THIS CAME OUT, I WAS PERFECTLY READY TO BELIEVE THAT THESE SCIENTISTS CARRIED OUT THESE EXPERIMENTS EXACTLY LIKE THEY SAID; THE NUMBERS WERE EXACTLY WHAT THEY GOT, BUT THAT THEY WERE ASSUMPTIONS THAT THEY SIMPLY GOT INCORRECT. AND SO THEIR CONCLUSION, ALTHOUGH IT WAS PERFECTLY CONSISTENT WITH THEIR DATA, JUST WASN'T THE RIGHT CONCLUSION.

THAT WAS -- THAT WAS MY FEELING AT THE TIME.

Q. WELL, THE -- THE CETUS SCIENTISTS IN THAT PAPER RAN CONTROLS

AND SUCH; IS THAT RIGHT?

A. OH, YEAH. OH . . . THEY DID EVERYTHING RIGHT, YES. YES, EVERYTHING JUST LIKE MY STUDENTS. YES, THEY HAD THE NUMBERS THERE. THEY DID ALL THE CONTROLS.

Q. WELL, WHY DIDN'T YOU BELIEVE, THEN, THAT THEY WERE GETTING THE KIND OF AMPLIFICATION THAT THEY THOUGHT THEY WERE REPORTING?

A. WELL, IT WAS -- IT WAS A MIND SET, I GUESS. IT WAS A BIAS, BECAUSE . . . THIS CONCEPT OF A TWO-PRIMER METHOD WAS ONE WHICH . . . I WAS AWARE OF FROM KHORANA'S PAPERS AND -- AND -- REALLY FOR TWO REASONS: FOR BOTH THEORETICAL REASONS AND ON PRACTICAL, HISTORICAL GROUNDS, IT WAS BELIEVED THAT IT SIMPLY -- IT SIMPLY COULD NOT WORK.

AND THE THEORETICAL GROUNDS ARE BASED ON -- THE TECHNICAL TERM IS RENATURATION KINETICS. SO, SORT OF, MY LEFT ARM IS ONE STRAND OF DNA (INDICATING) AND MY RIGHT ARM IS ANOTHER STRAND OF DNA (INDICATING).

DNA IS DOUBLE-STRANDED. AND WHAT THE . . . THE CONCEPT BEHIND PCR IS THAT WHAT'S SUPPOSED TO HAPPEN IS THAT TWO STRANDS COME APART (INDICATING) AND THEN YOU PUT A PRIMER HERE (INDICATING) AND YOU ADD EACH NUCLEOTIDE (INDICATING) AND HOOK IT UP AND COME RIGHT TO THE END, AND THE SAME THING ON THIS OTHER SIDE (INDICATING). AND THEN WHEN YOU FINISH WITH THAT, YOU HAVE FOUR. AND THEN THAT SEPARATES AND YOU HAVE EIGHT. THEN YOU HAVE 16. THEN YOU HAVE 32.

THE DIFFICULTY IS THAT -- THAT . . . THAT'S NOT WHAT

HAPPENS, BECAUSE -- BECAUSE THESE CHAINS COME TOGETHER FASTER (INDICATING) AND MORE EFFICIENTLY THAN YOU COULD EVER ZIP IT UP.

AND NOW ONE COULD GO INTO THE PHYSICAL CHEMISTRY, THE DELTA ENERGIES, BUT THE BASIC POINT IS THIS (INDICATING) -- SORRY -- THIS (INDICATING) IS -- IS FASTER AND MORE EFFICIENT THAN THIS (INDICATING).

SO JUST ON THEORETICAL GROUNDS, ON PURELY CALCULATION GROUNDS, IT SHOULDN'T WORK.

AND THEN, SECONDLY, WHEN YOU HAVE THE BEST LABORATORY IN THE WORLD, DR. KHORANA, WHOSE PUBLICATIONS INDICATE THAT THEY TRIED TO DO IT AND COULDN'T, THEN THAT SIMPLY -- SIMPLY VERIFIED THE MIND SET THAT WE ALL HAD THAT, ON THEORETICAL GROUNDS, IT CAN'T WORK.

SO WHEN CETUS COMES OUT WITH A PAPER AND IT SAYS, "OH, HERE ARE THE EXPERIMENTS WE DID, AND WE GOT EXPONENTIAL AMPLIFICATION," WE DISCUSSED IT IN DETAIL IN OUR LAB AND SAID, "WELL, WE CAN'T SEE THE FLAWS, WE CAN'T SEE WHAT THE INCORRECT ASSUMPTIONS ARE, BUT THEY'RE THERE SOMEWHERE," AND BASICALLY IGNORED IT.

Q. IT'S AN EXAMPLE OF WHAT YOU SOMETIMES HAVE DESCRIBED AS THE LITERATURE GETTING AHEAD OF THE FIELD?

A. YES. THAT'S A PHRASE THAT I'M KNOWN FOR. YOU WANT TO KNOW WHERE IT CAME FROM?

Q. PLEASE.

A. OKAY. WHEN I MENTIONED EARLIER THAT -- THAT, WHEN WE

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WERE -- AFTER DOING THE PROTEIN PART AND THE MESSENGER RNA PART, WE TRIED TO DEVELOP THE -- TO LEARN THE MACHINERY OF HOW A DNA MAKES AN RNA.

NOW, THAT'S BEEN WORKED OUT NOW IN RECENT YEARS, BUT -- BUT WE WERE A LITTLE PREMATURE WHEN I WAS TRYING TO DO IT.

BUT THERE WERE A NUMBER OF MAJOR LABORATORIES WORKING ON IT, AND WE ALL THOUGHT WE WERE GETTING RESULTS. WE THOUGHT WE HAD A NET SYNTHESIS OF BETA-GLOBIN MESSENGER RNA OFF OF THE CHROMOSOMES, THE CHROMATIN, THAT I ISOLATED FROM CELLS. AND WE WERE ALL PUBLISHING AND SORT OF RACING EACH OTHER BECAUSE THIS WAS ALL VERY EXCITING.

BUT . . . THEN AS WE WERE SORT OF LOOKING AT OUR -- OUR EXPERIMENTS, WE STARTED TO REALIZE THAT SOME OF OUR ASSUMPTIONS DIDN'T SEEM TO BE QUITE RIGHT.

AND SO ONE OF THE PEOPLE IN THE LAB, GROVER WILSON, WHO'S GONE ON TO BE VERY SUCCESSFUL, WENT BACK AND REALLY ANALYZED THAT WHOLE SYSTEM IN GREAT DETAIL AND DISCOVERED THAT THERE WASN'T JUST ONE ARTIFACT, THERE WERE TWO ARTIFACTS, AND THEY WERE BALANCING ARTIFACTS.

AND SO WHAT HAPPENS IS, WE ALL THOUGHT WE WERE GETTING A NET SYNTHESIS OF BETA-GLOBIN, BUT WHAT WE WERE REALLY GETTING IS . . . IS DATA WHICH COULD BE INTERPRETED THAT WAY BUT REALLY WASN'T.

AND I WAS GIVING A SEMINAR, I THINK IT WAS AT HARVARD OR M.I.T., BACK IN '74, '75, SOMEWHERE IN THERE, AND I -- AND I

WAS TALKING ABOUT THIS, AND I SAID -- AND I SAID, "THE LITERATURE HAS GOTTEN AHEAD OF THE FIELD." AND THAT PRODUCED A LAUGH, AND THEY . . . AND IT WAS A SPONTANEOUS STATEMENT.

AND WHAT I MEANT BY THAT WAS, WE WERE ALREADY PUBLISHING SUCCESSES AND WE REALLY HADN'T GOTTEN IT. WE JUST THOUGHT WE HAD BUT WE REALLY HADN'T GOTTEN IT.

IT'S LIKE SAYING, YOU KNOW, WE'VE LANDED SOMEBODY ON THE MOON, BUT IT . . . BUT . . . THE ROCKET HADN'T GOTTEN THERE YET.

SO THAT'S WHAT -- THAT'S WHAT HAPPENED.

AND BASICALLY THAT'S WHAT WE THOUGHT THIS WAS. I MEAN, THIS WAS THE LITERATURE HAD GOTTEN AHEAD OF THE FIELD. HERE WAS A STATEMENT SAYING THAT THEY HAD ENZYMATIC AMPLIFICATION OF BETA-GLOBIN GENETIC SEQUENCES.

Q. WELL, AT SOME POINT, YOU CHANGED YOUR MIND, I TAKE IT. YOU'RE NOW USING PCR.

A. YES, YES.

Q. HOW DID YOU COME TO BELIEVE THAT PCR, IN FACT, WORKS?

A. WELL, WHAT HAPPENED WAS THAT I WAS INVITED TO GIVE THE DAVIES LECTURES AT UNIVERSITY OF SAN FRANCISCO IN 1986, LATE OCTOBER, EARLY NOVEMBER 1986. AND BEFORE COMING OUT TO SAN FRANCISCO, A YOUNG LADY WHO'D BEEN A GRADUATE STUDENT, A VERY GOOD GRADUATE STUDENT OF MINE, WAS ACTUALLY WORKING AT CETUS. HER NAME WAS DR. YOWAN (PHONETIC) CHIANG, C-H-I-A-N-G.

YOWAN CALLED AND SAID, "WOULD YOU LIKE TO COME TO SAN

FRANCISCO? WOULD YOU LIKE TO COME BY AND VISIT MY FAMILY?

I SAID, "FINE."

SHE ASKED ME WHAT I THOUGHT ABOUT PCR, AND I SAID -- ABOUT THIS PAPER, AND I SAID, WELL, YOU KNOW -- SHE KNOWS I'M A SKEPTICAL SCIENTIST. I SAID, "I REALLY DON'T BELIEVE IT."

SHE SAID, "OH, NO, I'VE DONE IT WITH MY OWN HANDS. IT WORKS."

FOR YOWAN TO SAY, "I'VE DONE IT WITH MY OWN HANDS. THIS SYSTEM WORKS," MEANT THAT THAT WAS REALLY WORTH LOOKING INTO. I STILL DIDN'T BELIEVE IT, BUT IT WAS WORTH LOOKING INTO.

SO WHAT YOWAN DID IS, SHE ARRANGED FOR HENRY ERLICH AND JOHN SNINSKY TO COME TO MY LECTURE AT UNIVERSITY OF SAN FRANCISCO, AND THEN AFTERWARDS --

Q. AND THOSE ARE TWO CETUS SCIENTISTS?

A. YES. I'M SORRY. THOSE ARE TWO -- TWO CETUS SCIENTISTS WHO WERE INVOLVED IN THE PCR WORK.

THEY CAME TO MY LECTURE, AND AFTERWARDS WE STOOD OUT ON THE STEPS OF THE UNIVERSITY OF SAN FRANCISCO AND ARRANGED A COLLABORATION.

BUT I WAS CLEAR TO THEM THAT I WAS STILL VERY SKEPTICAL ABOUT THIS, AND SO WHAT I WANTED TO DO WAS BASICALLY TEST THEM FIRST.

AND SO WHAT WE DID IS THIS -- WE SENT THEM SOME CODED SAMPLES. WHAT A CODED SAMPLE IS -- MEANS IS, WE TOOK SOME CELLS WHERE EVERY CELL CONTAINED A GENE, AND THIS SPECIFIC GENE

HAPPENED TO BE A MARKER GENE, A NEOMYCIN SYNTHESIS, AND THEN DILUTED IT ONE TO TEN, ONE TO TEN, ONE TO TEN. SO WE SENT THEM TUBES THAT WERE ONE TO TEN, ONE TO A HUNDRED, ONE TO A THOUSAND, ONE TO 10,000, ONE TO A HUNDRED THOUSAND, ALONG WITH POSITIVE CONTROLS AND NEGATIVE CONTROLS, SCRAMBLED IT UP, JUST PUT ON LETTERS, SO THEY HAD NO WAY OF KNOWING WHAT WAS WHAT, SENT IT TO THEM.

STEVE SCHARF, WHO WAS THE SCIENTIST WHO DID IT, RAN THE PCR REACTION AND SENT BACK THE RESULTS ON A CELLULAR BLOT, ON AN X-RAY FILM, BY FEDERAL EXPRESS, AND WHEN -- I THINK IT WAS BY FEDERAL EXPRESS.

AND WHEN IT ARRIVED -- AND I REMEMBER VERY CLEARLY, WHEN I OPENED IT UP AND LOOKED AT THOSE AND SAW THEY HAD CORRECTLY IDENTIFIED EVERY ONE OF THEM, AT THAT POINT, I KNEW THAT PCR WORKED. I DIDN'T UNDERSTAND HOW IT COULD WORK AND HOW YOU COULD GET AROUND THIS PROBLEM (INDICATING), BUT IT WORKED.

AND SO WE IMMEDIATELY SET UP A COLLABORATION. INITIALLY, CETUS DID OUR PCR'S FOR US, BUT WITHIN A FEW MONTHS, WE HAD SET IT UP IN OUR LABORATORY, AND WE'VE DONE IT EVERY DAY SINCE.

Q. NOW, IF -- IF 15 YEARS BEFORE THIS, BACK IN 1970 OR 1971, YOU HAD BEEN TOLD THAT PCR COULD BE MADE TO WORK BACK AT THAT TIME, WOULD THAT HAVE BEEN SOMETHING THAT WOULD HAVE BEEN OF INTEREST TO YOU, GIVEN YOUR SITUATION IN THAT TIME PERIOD?

A. OH, IT WOULD HAVE BEEN OF ENORMOUS INTEREST. IT WOULD NOT

HAVE BEEN OF -- OF REAL PRACTICAL USE, TO ME, IN -- IN '71, PROBABLY, CERTAINLY BY '75, '76, WHEN I WAS DOING -- TRYING TO DO GENE TRANSFER KIND OF EXPERIMENTS. I'M NOT SURE '77. MAYBE . . . IT WAS -- IT WOULD HAVE BEEN OF SUFFICIENT INTEREST, I THINK, THOUGH, THAT MANY LABORATORIES WOULD HAVE ORIENTED THEIR -- THEIR EXPERIMENTS AROUND THE USE OF SUCH A SENSITIVE DETECTION SYSTEM, YES.

Q. NOW, GOING TO THIS LATER TIME PERIOD, THEN, 1976, COULD YOU HAVE USED PCR IN 1976?

A. OH, YES. OH, YES.

Q. NOW, WE'VE HEARD ABOUT THE NEED FOR PRIMERS TO DO PCR, AND YOU, OF COURSE, ARE AWARE OF THE NEED --

A. UH-HUH.

Q. -- TO HAVE THE TWO PRIMERS FOR THE TWO ENDS OF THE SEQUENCE.

A. RIGHT.

Q. COULD YOU HAVE GOTTEN THOSE PRIMERS IN 1976?

A. I WAS SYNTHESIZING PRIMERS WITH MY OWN HANDS IN 19 . . . IN 1966.

THE TWO MAJOR LABORATORIES WORKING ON THE GENETIC CODE WERE MARSHALL NIRENBERG'S LABORATORY AND GOBIND KHORANA'S LABORATORY.

KHORANA SYNTHESIZED THE VARIOUS TRIPLETS, THE OLIGONUCLEOTIDES, BIOCHEMICAL MEANS, AND WE DID IT BY ENZYMATIC MEANS. AND IN '66 -- '65-'66, I WAS THE PRIMARY PERSON IN THE NIRENBERG LABORATORY MAKING THOSE OLIGONUCLEOTIDES AND -- THEY

WERE RNA NUCLEOTIDES -- BUT MAKING THOSE -- THOSE NUCLEOTIDES, SO, YES.

IF A PROCEDURE IS SUFFICIENTLY VALUABLE, ONE WILL DO WHATEVER ONE HAS TO DO IN ORDER TO -- TO GET IT GOING. AND BY '75, '76, EVEN THOUGH IN ONE SENSE I HAD -- I HAD GIVEN MY LAB AWAY, I STILL CONTROLLED VERY SUBSTANTIAL RESOURCES. AND IF I HAD HAD ANY BELIEF THAT PCR WOULD WORK, THERE IS NO QUESTION IN '76 I COULD HAVE GOTTEN THE PRIMERS, I COULD HAVE GOTTEN THE ENZYMES, ET CETERA, YES.

Q. NOW, YOU'VE INDICATED THAT PCR IS USED IN YOUR LAB ON A REGULAR BASIS NOW?

A. YES.

Q. IS IT USED, FOR EXAMPLE, IN DIAGNOSING THE -- THIS -- OR NOT DIAGNOSING, BUT THE TESTING THE PROGRESS OF YOUR TREATMENT OF PEOPLE LIKE THIS GIRL WITH ADA DEFICIENCY?

A. OH, YES. OH, YES. THAT'S . . . THE PCR WAS WHAT WE USED TO FIRST DETECT THAT SHE HAD GENE-CORRECTED BLOOD CELLS IN HER BLOODSTREAM.

(PAUSE IN PROCEEDINGS)

THE WITNESS: AND . . . AND THAT THE NUMBER OF GENE-CORRECTED CELLS INCREASED. EACH TIME WE GAVE HER AN INFUSION OF GENE-CORRECTED CELLS, THE VALUE -- VALUE WENT UP.

AT THIS POINT, SHE IS -- HER PARENTS ARE DELIGHTED WITH HER. SHE IS THE -- IT'S THE FIRST TIME THAT SHE HAS REALLY BEEN HEALTHY FOR . . . HAS GONE FOR A LONG PERIOD OF TIME WITHOUT

GETTING SICK AND GETTING AN INFECTION. SHE HAS A NORMAL IMMUNE CELL COUNT FOR THE FIRST TIME IN HER LIFE. HER VARIOUS IMMUNE STUDIES ARE ALL -- ARE ALL IMPROVING.

WE REALLY ARE VERY PLEASED. IT DOES LOOK LIKE GENE THERAPY IS WORKING.

AND, AS I MENTIONED BEFORE, WE'VE STARTED OUR SECOND PATIENTS. WE STARTED TWO CANCER PATIENTS. AND WE ARE REALLY VERY HOPEFUL THAT WE'RE GOING TO BE ABLE TO DEVELOP REALLY NEW TREATMENTS FOR PRESENTLY INCURABLE DISEASES.

MR. PASAHOW: THAT CONCLUDES MY DIRECT EXAM, YOUR HONOR.

CROSS-EXAMINATION

BY MR. FIGG:

Q. GOOD MORNING, DR. ANDERSON.

A. HI, MR. FIGG.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DR. ANDERSON, THIS USE OF PCR THAT YOU REFERRED TO --

A. UH-HUH.

Q. -- DO I UNDERSTAND THAT YOUR FIRST PUBLICATION ON THE USE OF PCR WAS IN AN ARTICLE -- THE FIRST AUTHOR WAS KANTOFF, IN 1989?

A. THE ANSWER IS YES. KANTOFF HAD MORE THAN ONE, BUT, YES, WE'RE REFERRING TO THE SAME THING.

Q. OKAY. AND THAT WAS A PAPER REPORTING THE WORK THAT YOU HAD DONE IN COLLABORATION WITH DRS. ERLICH AND SNINSKY AND OTHERS AT

CETUS?

A. THAT IS CORRECT.

Q. AND YOU DIDN'T USE THE PCR TECHNIQUE PRIOR TO THE WORK REPORTED IN THAT PAPER; IS THAT CORRECT?

A. THAT IS CORRECT, YES.

Q. AND ALL OF THE WORK DONE IN THAT PROJECT THAT'S REPORTED IN THAT PAPER WAS DONE AT CETUS, ALL OF THE PCR WORK.

A. ALL OF THE P -- YES, YES, SIR.

Q. AS I RECALL, THAT PCR WORK IN THAT PAPER INVOLVED 35 CYCLES OF HEATING, COOLING, PRIMER EXTENSION, SO FORTH?

A. I DON'T REMEMBER EXACTLY, BUT THAT SOUNDS RIGHT, YES, SIR.

Q. UH-HUH. AND THAT WORK USED THIS ENZYME THAT WE'VE HEARD ABOUT BEFORE, THE TAQ POLYMERASE ENZYME?

A. YES, SIR.

Q. AND TAQ POLYMERASE IS A SPECIAL FORM OF AN ENZYME THAT'S RESISTANT TO HEAT?

A. YES.

Q. AM I CORRECT THAT YOU'VE NEVER USED PCR EMPLOYING AN ENZYME OTHER THAN TAQ?

A. IN OUR LABORATORY, THAT IS CORRECT, YES, SIR.

Q. YOU'VE NEVER DONE IT USING THE E. COLI POLYMERASE ENZYME THAT WE'VE HEARD TESTIMONY ABOUT BEFORE.

A. THAT IS CORRECT, YES, SIR.

Q. AND THIS PCR THAT WAS DESCRIBED IN YOUR PUBLICATION AND WHICH YOU'RE USING IN YOUR OWN WORK IS DONE ON THIS INSTRUMENT

CALLED A THERMOCYCLER?

A. YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) IN YOUR GENE THERAPY WORK THAT YOU -- YOU'VE DESCRIBED, WHICH SOUNDS LIKE VERY EXCITING WORK, WOULD -- WOULD A PCR REACTION INVOLVING TWO OR THREE OR FOUR CYCLES BE OF MUCH ASSISTANCE TO YOU IN THAT WORK?

A. WELL, THAT'S AN INTERESTING THOUGHT. TWO OR THREE OR FOUR.

YES, I THINK SO. CERTAINLY, TO BE ABLE TO GO OUT TO 15 OR 20 IS -- IS BETTER, BUT . . . BUT . . . IF ONE HAD -- HAD PCR, THAT -- THAT WAS WHAT THE OPTIMAL IS, AND THAT IS, YOU GET TWO, FOUR, EIGHT, 16. THAT WOULD MEAN THAT, AT FOUR CYCLES, YOU'D BE UP A LOG, A LITTLE OVER A LOG, AND THAT WOULD BE . . . THAT WOULD MEAN, THEN, THAT YOU COULD DETECT -- IF YOU WERE JUST UNDER THE RANGE OF DETECTION WITH A SOUTHERN BLOT, YOU COULD THEN PICK IT UP WITH A -- WITH A FOUR-CYCLE PCR.

SO, YES, THAT WOULD BE HELPFUL.

Q. I UNDERSTOOD YOU TO SAY THAT YOU'RE -- THE SOUTHERN BLOT LIMITATION IS SOMEWHERE IN THE RANGE OF ONE IN TEN TO ONE IN 20.

A. YES.

Q. AND WHAT YOU NEED FOR YOUR WORK GOES UP TO ONE IN A HUNDRED THOUSAND.

A. WE WOULD LIKE TO HAVE SOMETHING THAT GOES ONE IN A BILLION, BECAUSE -- BECAUSE WHAT HAPPENS IS THAT . . . AT LEAST IN THE MARKER STUDIES IN OUR CANCER PATIENTS, IS THAT THE CELLS BECAME

UNDETECTABLE AFTER ABOUT THREE WEEKS, BUT ONLY UNDETECTABLE IN ONE TO A HUNDRED THOUSAND. AND IF WE HAD A PROCEDURE THAT COULD DO ONE IN A MILLION, ONE IN A BILLION, THAT WOULD BE EVEN BETTER.

Q. UH-HUH. AND THIS -- THIS --

A. LET -- CAN I EXPLAIN WHY?

Q. SURE.

A. OKAY. THE REASON WHY IS THAT, SEE, WHAT -- WHAT YOU'RE TRYING TO DO IS TO -- IS TO TRANSFER GENES AS EFFICIENTLY AS YOU CAN. AND WHEN YOU'RE BELOW YOUR DETECTION LEVEL, YOU DON'T KNOW, WHEN YOU CHANGE A VARIABLE, IF YOU'VE HELPED AT ALL.

SO IF YOU'RE -- IF YOU'RE DOWN EVEN AT ONE IN A BILLION AND YOU DO SOMETHING AND NOW IT GOES UP TO -- TO ONE IN A MILLION, WELL, THAT'S -- THAT'S VERY HELPFUL AND YOU KNOW -- YOU KNOW YOU'RE ON THE RIGHT TRACK.

BUT IF YOU CAN'T DETECT IT AT ALL, THEN YOU DON'T KNOW, IF YOU CHANGED SOMETHING UP OR DOWN, WHAT'S HAPPENING.

SO -- SO THAT'S THE REASON WHY -- WHY THE MORE SENSITIVE IT IS, THE MORE USEFUL FOR OUR PURPOSES.

Q. UH-HUH.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) I BELIEVE THE NEXT PAPER THAT YOUR LABORATORY PUBLISHED THAT INVOLVED THE USE OF PCR WAS ONE BY MORGAN, CORNETTA AND ANDERSON?

A. YES.

Q. AND THAT ONE WAS PUBLISHED IN 1990.

A. YES, SIR.

Q. THAT ONE ALSO USED THE TAQ POLYMERASE --

A. YES.

Q. -- THE SPECIAL FORM OF ENZYME?

A. YES.

Q. AND IT ALSO USED THE THERMOCYCLER?

A. YES.

Q. AND IT ALSO USED SOMEWHERE ON THE ORDER OF 30 CYCLES OF AMPLIFICATION.

A. YES. WE'VE DROPPED IT TO 25 NOW, BUT, YES.

Q. YOU'VE NEVER USED AN AMPLIFICATION GOING THROUGH ONLY THREE OR FOUR CYCLES; HAVE YOU?

A. (SHAKING HEAD.) NO, SIR.

NOW . . . I'M . . . ONE OF THE THINGS WHICH DR. MORGAN DID IN CHARACTERIZING THE SYSTEM, OPTIMIZING THE SYSTEM IN OUR LAB, WAS TO GO THROUGH AND -- AND RUN IT AT VARIOUS LENGTHS OF CYCLE AND TO PLOT IT. SO, TECHNICALLY, YES, IT'S BEEN DONE, BUT ONLY AS PART OF AN OPTIMIZATION EXPERIMENT, NOT -- NOT IN REALITY.

Q. IT WAS A MULTIPLE CYCLE REACTION THAT YOU WERE JUST MONITORING THE PROGRESS OF.

A. YES, BUT -- I MEAN, IT WAS MONITORING IT SIMPLY SO, IN OUR OWN HANDS, WE SAW WHAT HAPPENED AFTER TWO CYCLES, SIX CYCLES, TEN CYCLES, 20. JUST TO PLOT THE CURVE.

Q. SURE.

A. A ONE-TIME --

Q. I UNDERSTAND.

A. A ONE-TIME EXPERIMENT.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) AND I UNDERSTAND YOUR LABORATORY -- WELL, YOU'VE ALREADY TESTIFIED THAT YOUR LABORATORY HAS COLLABORATED WITH THE CETUS SCIENTISTS TO -- TO BASICALLY LEARN HOW TO USE THE PCR TECHNIQUE TO OPTIMUM EFFICIENCY, I GUESS.

A. YES.

Q. AND YOU'VE ADOPTED PROTOCOLS AND PROCEDURES THAT HAVE BEEN DEVELOPED WITHIN THE CETUS LABORATORY.

A. YES.

Q. AND THOSE PROTOCOLS AND PROCEDURES THAT YOU'VE ADOPTED ARE THINGS THAT GO BEYOND WHAT ARE DESCRIBED IN, FOR EXAMPLE, THE SAIKI PAPER THAT YOU REFERRED TO.

A. YES.

Q. AND THEY GO BEYOND THE THINGS THAT ARE DESCRIBED IN THE '202 PATENT.

A. YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) IN THESE PCR EXPERIMENTS -- LET ME -- LET ME FOCUS ON ANOTHER ONE OF YOUR PAPERS:

THE NEXT PAPER, I THINK, THAT CAME OUT FROM YOUR LAB THAT DESCRIBES -- OR REFERS TO THE USE OF PCR WAS ONE IN WHICH

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DR. ROSENBERG WAS THE FIRST AUTHOR?

A. YES.

Q. IT LOOKS LIKE IT HAS ABOUT 15 AUTHORS.

A. I THINK IT'S 18. YES, THAT'S RIGHT.

Q. AND THAT ONE WAS ALSO PUBLISHED IN 1990.

A. YES.

Q. AND THESE TECHNIQUES THAT YOU'RE PUBLISHING ON USE GENOMIC DNA AS THE TARGET; IS THAT RIGHT?

A. YES.

Q. AND GENOMIC DNA IS ALL OF THE DNA IN THE CELLS.

A. THAT IS CORRECT.

Q. SO WE'VE HEARD DR. KORNBERG TESTIFY, I THINK, THAT THE ESTIMATES ARE THAT THERE ARE BETWEEN 10,000 AND A HUNDRED THOUSAND GENES IN EACH OF THE CELLS.

A. YES, I AGREE WITH THAT.

Q. YEAH.

YOU'VE NEVER USED THE PCR TECHNIQUE ON A SINGLE MOLECULE; HAVE YOU?

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) IN OTHER WORDS, A DISCRETE DNA SEQUENCE.

A. A PURE MOLECULE --

Q. RIGHT.

A. -- OF A FRAGMENT.

Q. RIGHT.

A. EXCEPT FOR CHARACTERIZATION KINDS OF STUDIES, NO.

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Q. NOW, YOU TESTIFIED ABOUT YOUR FAMILIARITY WITH THE HYBRIDIZATION TECHNIQUE.

A. YES.

Q. YOU REFERRED SPECIFICALLY TO SOUTHERN BLOTTING.

A. YES.

Q. INCIDENTALLY, DOCTOR, HAVE YOU REVIEWED THE PATENTS THAT ARE IN ISSUE IN THIS LAWSUIT, THE '202 AND THE '195 PATENTS?

A. I DID SEVERAL MONTHS AGO PRIOR TO GIVING A DEPOSITION. I'M NOT A PATENT EXPERT --

Q. NO, I UNDERSTAND.

A. -- BUT, YES, I THINK THE -- THE . . . THE RELEVANT PARTS OF THE PATENTS I THINK I'M FAMILIAR WITH.

Q. WELL, JUST AS A BACKGROUND, IS -- DO YOU UNDERSTAND THAT THE '195 PATENT CLAIMS A PROCESS FOR FIRST AMPLIFYING WITH PCR AND THEN DETECTING WITH HYBRIDIZATION?

A. YES.

Q. AND THIS DETECTING WITH HYBRIDIZATION IS THE SAME DETECTION TECHNIQUE THAT YOU WERE DISCUSSING WITH MR. PASAHOW; IS THAT RIGHT?

A. THAT'S A LITTLE VAGUE, BUT WE KNOW WHAT WE'RE TALKING ABOUT, YES.

Q. YEAH. WELL, IN OTHER WORDS, YOU TAKE A PIECE OF DNA --

A. YES.

Q. -- THAT'S BEEN LABELED WITH SOMETHING --

A. RIGHT.

Q. -- AND YOU DETERMINE WHETHER OR NOT IT WILL HYBRIDIZE --

A. YES.

Q. -- TO A SAMPLE.

A. UH-HUH.

Q. AND YOU -- YOU'VE USED HYBRIDIZATION TO DETECT THE PRESENCE OF SPECIFIC DNA SEQUENCES IN MIXTURES OF DNA FOR SEVERAL DECADES NOW, I GUESS. AT LEAST SINCE THE MID-'70'S.

A. OKAY. THE -- USED WHAT?

Q. HYBRIDIZATION.

A. OH, HYBRID -- OH, YES, YES. FOR . . . THIS IS -- SINCE '71. 20 YEARS, YES.

Q. UH-HUH. NOW, AM I CORRECT THAT YOU -- BACK IN THE MID-'70'S, YOU WERE STUDYING TRANSFER OF GENES INTO CELL CULTURES THAT YOU COULD GROW IN PETRI DISHES?

A. YES, SIR.

Q. AND ONE OF THE TECHNIQUES YOU USED WAS TO . . . CLONE A GENE INTO A CELL, IF I CAN USE THAT TERM; IS THAT RIGHT?

A. IT'S NOT QUITE RIGHT, BECAUSE CLONE -- AS YOU KNOW, THERE'S SEVERAL WAYS OF CLONING GENES.

BUT GO AHEAD. I THINK THE ANSWER IS GOING TO END UP BEING YES, IN ANY CASE.

Q. WELL, YOU INSERT A GENE INTO A CELL.

A. YES. INSERT A GENE INTO A CELL, YES, THAT'S RIGHT.

Q. AND THE POINT OF THAT IS, THE GENE WILL REPLICATE AS THE CELL REPLICATES.

A. YES, EXACTLY RIGHT.

Q. AND AM I CORRECT THAT YOU WOULD THEN GROW THOSE CELLS AND AMPLIFY THEIR NUMBERS?

A. THAT IS CORRECT.

Q. AND IN AMPLIFYING THEIR NUMBERS, YOU WERE AMPLIFYING THAT GENE THAT YOU INSERTED INTO IT.

A. THAT IS CORRECT. IT'S A FORM OF AMPLIFICATION, CORRECT.

Q. AND ONE OF THE REASONS THAT YOU AMPLIFIED THE GENE WAS SO THAT YOU COULD THEN INCREASE THE SENSITIVITY OF YOUR HYBRIDIZATION TECHNIQUE.

A. THAT IS EXACTLY RIGHT. IF YOU MICROINJECT A GENE INTO ONE CELL, THAT IS -- THAT IS VERY DIFFICULT. IT CAN ACTUALLY BE DONE NOW WITH PCR, BUT CERTAINLY NOT AT THAT POINT.

BUT THEN, BY HAVING THE CELL GROW TO A BILLION CELLS, IT IS -- NOW YOU CAN USE A SIMPLE SOUTHERN BLOT, AND IT WORKS FINE.

Q. YES. SO YOU, IN EFFECT, BACK IN THE '70'S WERE COMBINING AN AMPLIFICATION PROCEDURE WITH A PROBE HYBRIDIZATION --

A. OH, YES.

Q. -- DETECTION PROCEDURE.

A. OH, YES. THAT IS PROBABLY THE -- HOW CAN I PUT IT? -- THE CENTRAL PART OF -- FOR THE LAST 15 YEARS OF MY LABORATORY, YES.

Q. DOCTOR, IN YOUR OPINION, WOULD IT HAVE BEEN OBVIOUS TO ONE OF YOUR POST-DOCTORAL STUDENTS BACK IN THE LATE '70'S, HAD THAT STUDENT KNOWN ABOUT WHAT WE'RE NOW CALLING PCR --

A. UH-HUH.

Q. -- WOULD IT HAVE BEEN OBVIOUS TO HAVE USED PROBE HYBRIDIZATION TO DETECT THE PRODUCT RESULTING FROM PCR?

A. YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) NOW, YOU REFERRED TO YOUR READING OF VARIOUS LITERATURE FROM DR. KHORANA'S LABORATORY.

I TAKE IT THAT YOU DON'T HAVE A SPECIFIC RECOLLECTION TODAY THAT YOU READ THE KLEPPE AND PANET PAPERS BACK IN 1972, 1974.

A. THAT IS CORRECT. I'VE -- I'M SURE I DID, BECAUSE I READ EVERY PAPER AS IT CAME OUT, UNTIL WE CAME CONVINCED OR I BECAME CONVINCED THAT RECOMBINANT DNA WOULD BE THE TECHNOLOGY. THEN I STOPPED DOING THAT.

AS YOU KNOW, DR. KHORANA PUBLISHED MANY, MANY PAPERS. BUT I DO NOT HAVE A SPECIFIC RECOLLECTION OF THE KLEPPE AND PANET PAPERS.

Q. YES, SIR.

AND WHEN YOU SAY RECOMBINANT DNA, YOU'RE TALKING ABOUT -- USING A SIMPLER WORD, PERHAPS -- GENE CLONING.

A. YES. GENE CLONING, YES.

Q. YES.

A. YES.

Q. AND YOU RECOGNIZED THAT GENE CLONING WAS GOING TO BE A -- AN EFFECTIVE WAY OF AMPLIFYING DNA IN LIVING CELLS.

A. THAT'S NOT QUITE CORRECT. A . . . GENE CLONING TO AMPLIFY DNA IS DONE IN BACTERIAL CELLS AND -- AND, YES, THAT'S A LIVING CELL, BUT ONE USUALLY REFERS TO LIVING CELLS AS BEING ANIMAL CELLS, AND ONE DOES NOT TECHNICALLY AMPLIFY -- DOES NOT USE THE CLONING PROCEDURES TO AMPLIFY A GENE IN A -- IN A MAMMALIAN CELL.

Q. OKAY. YOU WERE . . . GOING BACK TO -- TO THE THINGS FROM DR. KHORANA'S LAB WHICH YOU'VE READ, DO YOU BELIEVE YOU READ DR. KHORANA'S NSF GRANT APPLICATION?

A. OH, I'M SURE I DID NOT. I WOULD HAVE HAD NO . . . I --

Q. YOU WOULD HAVE HAD NO REASON TO HAVE READ THAT.

A. NOT ONLY NO REASON; I WOULD HAVE HAD NO OPPORTUNITY. IT WOULD NOT HAVE BEEN APPROPRIATE.

Q. OKAY. DOCTOR, AM I -- DID I UNDERSTAND YOU CORRECTLY THAT YOU -- IN YOUR OPINION, THE KHORANA PAPERS, THE PANET AND THE KLEPPE PAPERS, DO DESCRIBE A SIMPLIFIED PCR TECHNIQUE?

A. NO.

(PAUSE IN PROCEEDINGS)

THE WITNESS: IN MY --

Q. (BY MR. FIGG) DID -- LET ME REPHRASE THE QUESTION.

A. OKAY.

Q. DO THEY DESCRIBE, IN A -- IN A VERY SIMPLIFIED WAY, WHAT -- WHAT NOW MAY BE CALLED PCR, WHAT WE NOW KNOW AS PCR?

A. NO, SIR, BECAUSE THEY . . . THEY REALLY LEAVE OUT A VITAL INSIGHT -- IN FACT, THE VITAL INSIGHT THAT REALLY IS -- IS THE

CORE OF WHAT PCR REALLY IS.

AND LET ME EXPLAIN: THE . . . THE PROBLEM IS THAT THIS IS WHAT YOU HAVE (INDICATING). THE SECOND STRAND CLAMPS DOWN BEFORE THE FIRST STRAND CAN FINISH OUT (INDICATING).

AND WHAT PCR REQUIRES IS -- IS A -- IS AN INSIGHT THAT KARY MULLIS HAD, AND THAT IS TO CREATE, FOR A LACK OF A BETTER WORD, A TIME WINDOW.

NOW, WHAT'S A TIME WINDOW? A TIME WINDOW IS THIS: THESE ARE DOUBLE-STRANDED DNA (INDICATING), COMES APART, COMES BACK TOGETHER (INDICATING). THAT HAPPENS TOO FAST FOR THIS (INDICATING) TO COME UP. MAYBE ONE IN A THOUSAND TIMES, MAYBE ONE IN 10,000, MAYBE ONE IN A HUNDRED THOUSAND. BUT IT REALLY IS NOT FAST ENOUGH.

HOW DO YOU KEEP THE SECOND STRAND FROM COMING OVER? WELL, THE WAY THAT EVERYBODY TRIED TO DO IT, AS FAR AS I KNOW FROM THE -- FROM THE PUBLICATIONS, IS TO -- IS TO SEPARATE THE STRANDS, PUT THEM IN SEPARATE TEST TUBES.

WHAT DR. MULLIS DID WAS SOMETHING THAT I THINK IS REALLY -- REALLY VERY BRILLIANT, AND THAT IS, HE CREATED A TIME WINDOW.

WHAT HE DID ESSENTIALLY WAS THIS: INSTEAD OF THAT (INDICATING), HE DID THIS (INDICATING). HE KINETICALLY MOVED THE SECOND STRAND COMPLETELY AWAY FROM THE FIRST STRAND TO GIVE IT LONG ENOUGH FOR THIS (INDICATING) TO COME TO THE END.

THAT IS THE -- IS THE -- IS THE VITAL INSIGHT, AND IF

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IT DOESN'T HAVE THAT, IT ISN'T PCR.

NOW, HOW DID HE DO IT? THE WAY HE DID THIS WAS AS FOLLOWS:

THE FIRST PROBLEM IS, IF YOU JUST THINK OF A WHOLE BUNCH OF PEOPLE LINED UP AND THEY COME TOGETHER, AND YOU HEAT AND THOSE STRANDS COME APART, YOU BUMP INTO THE NEXT PERSON.

WELL, THIS STRAND (INDICATING) IS JUST AS GOOD AS TO HYBRIDIZE WITH AS THIS STRAND WAS (INDICATING).

SO THE FIRST . . . THE FIRST ELEMENT IS TO -- IS TO DEVELOP THE CONDITIONS WHERE, WHEN THESE (INDICATING) COME APART, THEY DON'T HIT ANYTHING ELSE. SO THEY SORT OF FLOAT OUT LIKE THIS (INDICATING).

THE SECOND PART IS TO HAVE THE ENZYMES, THE -- THE PRIMERS, THE NUCLEOTIDES LINED UP SO, AS SOON AS IT STARTS TO COOL AGAIN, THERE IS -- THERE IS A WINDOW, SEE, BETWEEN THIS (INDICATING) AND THIS (INDICATING). THAT'S THE TIME WINDOW. AND IN THAT PERIOD OF TIME, TO HAVE EVERYTHING READY SO THAT THIS STRAND (INDICATING) ZIPS UP.

THAT TIME WINDOW IS SECONDS TO MINUTES.

THAT IS A -- IS A CONCEPT THAT IS NOWHERE IN THE LITERATURE. THAT -- IT'S MY OPINION THAT THAT WAS -- KARY MULLIS WAS THE FIRST PERSON TO CONCEIVE OF THAT CONCEPT AND TO CREATE THE CONDITIONS FOR A TIME WINDOW.

IT'S THIS (INDICATING) VERSUS THIS (INDICATING). AND IT'S THIS WINDOW THAT ALLOWS PCR. WITHOUT THAT, IT IS NOT PCR.

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DR. KHORANA, FROM WHAT I CAN GATHER, NEVER TAUGHT PCR; NEVER CONCEIVED OF WHAT IS THE CRITICAL ELEMENT IN PCR.

Q. DOCTOR, THIS CRITICAL ELEMENT THAT YOU'RE REFERRING TO -- I THINK YOU REFERRED TO TWO -- ONE IS DR. MULLIS, IN YOUR VIEW, DEVISED A WAY OF KEEPING THE TEMPLATE STRANDS APART?

A. ALL PART OF THE SAME THING.

Q. WELL, LET ME ASK YOU: WAS THAT ACCOMPLISHED BY ADJUSTING THE CONCENTRATION?

A. NO. YOU SEE, WHAT MAKES IT --

Q. WELL --

A. WHAT MAKES THIS DIFFICULT TO UNDERSTAND -- AND I'VE BEEN SITTING IN COURT LISTENING TO THIS. WHAT MAKES THIS DIFFICULT -- AND I'M SURE THE JURY MUST BE CONFUSED: WHAT'S PCR? WHAT'S NOT PCR?

PCR IS A THREE-DIMENSIONAL REACTION THAT TAKES PLACE OVER TIME, SO IT'S REALLY FOUR DIMENSIONS. AND WHEN YOU TRY TO EXPLAIN IT ON A TWO-DIMENSIONAL PIECE OF PAPER, OR A CHART, OR, YOU KNOW, A VELCRO -- THAT FANCY WORD YOU'VE GOT, THAT I COULD JUST SEE THE EDGE OF -- IT'S CONFUSING, BECAUSE -- BECAUSE YOU HAVE TO -- TO VISUALIZE FOUR DIMENSIONS RATHER THAN TWO DIMENSIONS.

SO ANY TIME THAT YOU SAY, "WELL, IS IT BECAUSE YOU HAVE EXCESS PRIMER, OR IS IT CONCENTRATION," IT'S NOT. IT'S THE WHOLE SET OF CONDITIONS. AND THOSE CONDITIONS CAN VARY. ANY SINGLE ONE CAN VARY UP AND DOWN.

IT'S THE WHOLE SET THAT CREATES A TIME WINDOW. IT'S THE TIME WINDOW THAT -- THAT IS CRITICAL.

SO IT'S NOT THE -- THE TWO THINGS. IT'S ALL ONE. BUT EVERY PART OF THAT IS CRITICAL TO GET PCR TO WORK.

IT LOOKS GOOD ON A PIECE OF PAPER AND YOU CAN PUT MODELS, BUT IT DOESN'T HAPPEN IN REALITY.

Q. SO THE CONCENTRATION IS CRITICAL, THE RATIO OF PRIMERS IS CRITICAL, THE --

A. THE TEMPERATURE, THE TIMING --

Q. -- TEMPERATURE, ALL THE --

A. -- THE WAY YOU ADD THINGS, ALL OF -- IN A WAY TO PRODUCE THE CONDITIONS SUCH THAT YOU DO GET TO THE END AND, THEREFORE, TECHNICALLY SATISFY THE CLAIM THAT THE PRODUCT OF THE FIRST THREE REACTIONS ACTS AS A TEMPLATE FOR THE SECOND. THAT'S THE VITAL INSIGHT THAT HAS TO BE THERE OR IT'S NOT PCR.

Q. DOCTOR, GOING BACK TO MY ORIGINAL QUESTION:

DO YOU . . . DO YOU RECALL THAT I ASKED YOU A SIMILAR QUESTION IN YOUR DEPOSITION?

A. YES, YOU CERTAINLY DID.

Q. I ASKED YOU:

"IS IT YOUR UNDERSTANDING THAT THE KHORANA PAPERS THAT YOU HAVE REVIEWED FROM THE EARLY '70'S DO DESCRIBE THE PCR REACTION?"

A. YES.

Q. AND DO YOU RECALL THAT YOUR ANSWER WAS:

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"THEY DESCRIBE IN A VERY OVERSIMPLIFIED WAY WHAT CAN NOW BE CALLED, BASED ON WHAT WE NOW KNOW, PCR."

A. AND FURTHER THAN THAT, I SAID AT ANOTHER POINT THAT I BELIEVE THAT DR. KHORANA HAD THE FULL CONCEPT IN HIS MIND. AND ON TWO OTHER PLACES, IF YOU'LL NOTICE -- PAGE 63, 64, AND AGAIN ON PAGE 103 -- I SAID I STILL DON'T BELIEVE PCR WORKS. I DON'T UNDERSTAND IT.

Q. UH-HUH.

A. AND THAT WAS TRUE.

BUT WHAT HAPPENED WAS THAT, AFTER THAT DEPOSITION ON NOVEMBER 4TH, AND I WENT BACK AND I REALIZED I WAS GOING TO BE SITTING HERE IN A REAL COURT -- I'VE NEVER BEEN IN A REAL COURT BEFORE. THIS IS THE FIRST TIME. IT'S REALLY SORT OF NEAT WITH A JUDGE HERE, AND A JURY AND EVERYTHING.

(LAUGHTER)

THE WITNESS: AND I REALIZED THAT I WAS GOING TO BE FACING YOU, AND YOU'RE A BRILLIANT CROSS-EXAMINER, AND HERE, I'M SUPPOSED TO BE UP HERE TALKING ABOUT PCR AND I DON'T EVEN UNDERSTAND IT.

SO I REALLY STARTED TO THINK ABOUT IT. AND I -- AND I ACTUALLY TALKED WITH -- WITH KARY MULLIS AND OTHERS, AND I FINALLY REALIZED WHAT I DIDN'T UNDERSTAND, AND THAT IS THIS WHOLE CONCEPT OF A TIME WINDOW THAT ONLY LASTS SECONDS TO MINUTES.

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AND SO -- SO, YES, I AM CHANGING WHAT I SAID IN THE DEPOSITION. I DO NOT BELIEVE THAT DR. KHORANA EVER UNDERSTOOD THAT CONCEPT, AND I DID NOT UNDERSTAND THAT CONCEPT, AND THAT'S WHY I SAID I DON'T BELIEVE IT.

Q. SO YOU'VE -- YOU'VE LEARNED ABOUT ALL OF THAT SINCE -- SINCE WE HAD OUR DEPOSITION.

A. WELL, "LEARNED" ISN'T QUITE RIGHT. I'VE BEEN IN COMPLETE TEST HYBRIDIZATION FOR 20 YEARS. I'VE PUBLISHED PAPERS ON THEORETICAL ASPECTS, PRACTICAL ASPECTS.

BUT, YOU KNOW, YOU DON'T REALLY SIT DOWN AND THINK ABOUT SOMETHING -- I MEAN REALLY THINK ABOUT IT -- UNTIL YOU HAVE TO. AND FACING YOU MEANT I HAD TO.

SO -- SO -- SO, YES, "LEARNED" IN THE SENSE OF APPRECIATED WHAT THAT -- WHAT THAT -- THAT VITAL INSIGHT WAS. YES, THAT IS TRUE.

Q. WELL, DOCTOR, HAVE YOU READ THE '202 PATENT TO SEE IF YOU CAN FIGURE OUT PRECISELY WHAT THIS COMBINATION OF CONDITIONS IS?

A. YES. I -- I'VE -- I DID THAT ONCE I . . . REALIZED THAT I'D READ IT THE FIRST TIME NAIVELY. I MEAN, I HADN'T APPRECIATED WHAT WAS THERE.

Q. WOULD YOU AGREE WITH ME THAT EACH OF THOSE CRITICAL CONDITIONS THAT YOU'RE REFERRING TO IS NOT SPELLED OUT IN ANY WAY IN ANY OF THE CLAIMS OF THE '202 PATENT?

A. NO. WHAT THE -- WHAT THE CLAIMS OF THE '202 PATENT SAY IS IN THE -- IN THE FIRST A, 1-A, IT SAYS "FOR CONDITIONS THAT WILL

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GIVE" . . . THAT WILL GIVE THE PRODUCT OF THE FIRST REACTION ACTING AS TEMPLATE FOR THE SECOND. THEN DOWN IN C, IT SAYS THAT THE PRODUCT DOES ACT AS A TEMPLATE.

NOW, THE ONLY WAY THAT CAN HAPPEN IN REALITY IS TO HAVE -- IS TO HAVE A TIME WINDOW. YOU'VE GOT TO KEEP THE OTHER STRAND AWAY.

SO THOSE CONDITIONS . . . THE CLAIM SAYS THOSE CONDITIONS, AND THE ONLY WAY YOU CAN DO IT IS TO GET THE STRAND OUT OF THERE.

Q. UH-HUH.

A. AND THE EXAMPLES THEN EXPLAIN EXACTLY HOW TO DO THAT.

Q. SO THE CLAIM SAYS "UNDER ANY CONDITIONS THAT WORK."

A. UNDER ANY CONDITIONS THAT -- THAT WILL GIVE YOU A TIME WINDOW, YES, YES. TO MY MIND -- AND MAYBE THIS ISN'T WHAT OTHERS THINK, BUT TO MY MIND, THAT -- THAT IS WHAT PCR IS. THAT'S WHAT -- THAT'S WHAT DR. MULLIS TAUGHT THAT NO ONE ELSE HAS EVER TAUGHT.

AND I'LL CHANGE SOMETHING ELSE THAT I SAID IN MY DEPOSITION: YOU WENT THROUGH AND SAID COULD --

Q. WELL, MAYBE WE SHOULD JUST PROCEED --

A. OH, I'M SORRY.

Q. -- ON A QUESTION AND ANSWER BASIS HERE, DOCTOR.

A. OKAY. I'M SORRY.

Q. MAYBE THE NEXT QUESTION I'M GOING TO ASK YOU WILL BE SOMETHING YOU WANT TO CHANGE.

A. OKAY.

Q. DOCTOR, YOU REFERRED TO THIS -- THIS PROBLEM OF RENATURATION KINETICS.

A. YES.

Q. AND I THINK THAT'S WHAT YOU'VE JUST BEEN DISCUSSING.

A. UH-HUH, YES.

Q. IN OTHER WORDS, THE QUESTION OF WHETHER YOU CAN GET THE PRIMERS ANNEALED TO THE TEMPLATE BEFORE THE TEMPLATES RE-ANNEAL.

A. NO. NO, NOT THE PRIMER ANNEALED. THE PRIMER CAN ANNEAL OKAY, BECAUSE YOU'VE GOT THE PRIMER AND THE TEMPLATE TOGETHER BEFORE YOU EVER ADD THE ENZYME.

IT'S THAT -- IT'S THAT TIME FRAME. SEE, YOUR VELCRO THING REALLY IS MISLEADING BECAUSE -- BECAUSE . . . I DON'T MEAN DISHONESTLY, BUT IT'S MISLEADING, BECAUSE WHAT YOU HAD THERE, FROM WHAT I COULD SEE LOOKING AROUND THE SIDE, IS, YOU'VE GOT THE TEMPLATE, AND THEN YOU HAD YOUR PRIMER, AND THEN YOU HAD ALL THE SUBSTRATE AS ONE UNIT THAT YOU JUST SORT OF SET IN THERE, BUT THAT ISN'T WHAT HAPPENS.

YOU'VE GOT TO ADD ONE BASE AT A TIME. IT GOES ONE, ONE --

Q. DID YOU HEAR --

A. -- AND IN THAT LENGTH OF TIME, THE TWO HAVE COME BACK TOGETHER.

Q. DID YOU HEAR DR. KORNBERG'S EXPLANATION OF THAT CHART?

A. NO. I DID READ THROUGH HIS TESTIMONY, AND I FEEL DR.

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KORNBERG -- DR. KORNBERG IS ONE OF MY IDOLS. HE IS ONE OF THE GREAT SCIENTISTS IN THE LAST 40 YEARS.

Q. WELL --

A. IN ALL HONESTY, I DON'T THINK HE APPRECIATES THE TIME WINDOW, I REALLY DON'T.

Q. YOU DID HEAR DR. KORNBERG EXPLAIN --

A. I DIDN'T HEAR; I READ.

Q. -- THAT THESE NUCLEOTIDES GO IN ONE AT A TIME.

A. OH, YES.

Q. WHEN HE WAS EXPLAINING THE CHART, HE EXPLAINED THAT THAT WAS WHAT IT WAS.

A. OH, YES. BUT, NONETHELESS, IF I WAS SITTING IN THE JURY BOX, AND YOU SAID EACH TIME HERE'S A PRIME, AND HERE IT IS TO THE END, I THINK I COULD BE CONFUSED SAYING, "WELL, THIS IS -- ISN'T THIS REALLY PCR? ISN'T THIS REALLY THE FIRST STEP OF PCR?", AND IT'S NOT.

Q. WELL, DOCTOR, I UNDERSTAND THAT, IN YOUR OWN WORK, YOU HAVE -- BACK IN THE LATE '70'S, THAT YOU HAD DONE EXPERIMENTS OF ANNEALING A PRIMER TO A STRAND OF --

A. OH, YES.

Q. -- DNA AND EXTENDING IT?

A. THOUSANDS OF TIMES, YES.

Q. AND YOU'VE DONE THAT WITH DOUBLE-STRANDED DNA.

A. YES.

Q. YOU DID IT WITH A SYSTEM FOR MAKING ONE OF THESE

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HYBRIDIZATION PROBES; IS THAT RIGHT?

A. YES, INDEED. YES, INDEED.

Q. AND THE WAY YOU DID THAT EXPERIMENT WAS TO TAKE THE DOUBLE-STRANDED DNA AND PUT IT IN A SOLUTION; IS THAT CORRECT?

A. UH-HUH. YES, UH-HUH.

Q. AND YOU HEATED IT --

A. UH-HUH.

Q. -- TO SEPARATE THE PRIME -- THE TEMPLATE STRANDS.

A. YEAH.

Q. AND YOU PUT PRIMER IN THERE.

A. YES.

Q. IN AN EXCESS.

A. YES.

Q. AND THE PRIMER ANNEALED.

A. YES.

Q. AND YOU PUT THE ENZYME IN.

A. YES.

Q. AND THE ENZYME EXTENDED --

A. NO.

Q. -- AND MADE A TEMPLATE.

A. (INDICATING). THAT'S WHAT HAPPENED. IT GOES PART WAY. YOU CAN ALWAYS GET IT TO GO PART WAY, BUT IF YOU DON'T CREATE A TIME WINDOW, IT ONLY GOES PART WAY.

Q. DOCTOR --

A. YOU NEVER GO TO THE END. YOU CANNOT HAVE PCR.

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Q. THE POLYMERASE IN THOSE REACTIONS, YOU GOT THEM TO MAKE PROBES THAT WERE UP TO A THOUSAND BASES IN LENGTH.

A. OH, SURE. OH, SURE. YOU CAN GET THEM -- YOU CAN GET THEM TO GO TO A THOUSAND. IF YOU START WITH . . . WITH A TEMPLATE THAT'S 1500, YOU CAN GO TO A THOUSAND, SURE.

Q. UH-HUH.

A. BUT YOU CAN'T GET TO THE END UNLESS YOU SEPARATE THAT STRAND.

Q. YEAH. BUT YOU WERE ABLE TO GET IT TO GO TO A THOUSAND, THOUGH.

A. OH, YES. OH, YES, YES.

Q. THE END OF THAT SITUATION -- OF THAT PARTICULAR EXPERIMENT WE WERE TALKING ABOUT MIGHT BE SEVERAL MORE THOUSAND DOWN THE WAY.

A. (NODDING HEAD.) YEAH, RIGHT.

Q. YEAH.

A. RIGHT. NO, THERE'S NO QUESTION THAT YOU CAN GET A POLYMERASE TO MAKE A CHAIN THAT'S OUT HUNDREDS, A THOUSAND, THAT IS CORRECT.

Q. AND --

A. THE REASON THAT -- THE REASON THAT THERE'S THESE PROBLEMS IN VITRO -- "IN VITRO" IS A TECHNICAL TERM -- IN A TEST TUBE. THESE ENZYMES AREN'T -- AREN'T CREATED BY . . . A BIOCHEMICAL COMPANY. THEY EXIST IN THE CELLS OF OUR BODIES, IN ANIMAL CELLS.

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AND IN THAT ENVIRONMENT, THE ENZYMES ARE DESIGNED TO WORK. WHEN YOU TAKE THEM OUT AND PURIFY THEM AND PUT THEM INTO A TEST TUBE, THAT'S A VERY ARTIFICIAL ENVIRONMENT.

SO THAT -- THAT . . . EVEN THOUGH WHAT THEY -- THEY WANT TO DO IS TO GO ALL THE WAY TO THE END, IT'S SUCH AN ARTIFICIAL ENVIRONMENT, THEY DON'T DO IT UNLESS YOU CREATE UNIQUE CONDITIONS TO -- TO LET THEM.

BUT THERE'S NO QUESTION YOU CAN GO A THOUSAND BASES WITH THESE ENZYMES, YES.

Q. OKAY. THEY DIDN'T GO TO THE END OF THESE 4,000 OR 3,000 --

A. RIGHT, RIGHT.

Q. -- BUT THEY WENT A THOUSAND DOWN THE PIKE.

A. YES. YES.

Q. AND . . . YOUR POST-DOCTORAL STUDENTS WERE DOING -- WERE CARRYING OUT THOSE EXPERIMENTS IN THE LATE 1970'S; IS THAT RIGHT?

A. OH, YES.

Q. AND THEY WERE WORKING OUT THE CONDITIONS FOR DOING IT.

A. YES.

Q. AND AMONG THE CONDITIONS THEY WERE USING FOR THAT WERE TO . . . AFTER ADDING THE PRIMERS AND DENATURING THE DNA, TO QUICKLY CHILL THE DNA?

A. THAT'S -- YES, YES.

Q. AND THAT WAS A WELL-KNOWN TECHNIQUE --

A. YES.

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Q. -- IN THOSE DAYS TO OPTIMIZE GETTING THE PRIMER TO STICK ON THE --

A. YES.

Q. -- DOUBLE-STRANDED DNA.

A. YES. THAT GUARANTEES THE . . . YOU CAN NEVER, NEVER DO A PCR BY CHILLING THE REACTION. THAT GUARANTEES THAT YOU'VE CLOSED YOUR TIME WINDOW.

Q. SO IF YOU CHILL A PCR REACTION, IT WON'T WORK?

A. WELL, IT'S NOT A PCR REACTION ANYMORE, BECAUSE -- NO, IT WON'T WORK, BECAUSE THERE'S NO TIME WINDOW, BUT -- BUT THOSE CHAINS ARE ALREADY BACK TOGETHER.

NOW, IT DEPENDS -- DEPENDS WHAT YOU MEAN BY "CHILL," OF COURSE. JUST LIKE EVERYTHING ELSE, ONE CANNOT FOCUS ON ONE CONDITION, BECAUSE IT'S THE WHOLE GROUP.

YOU COULD, IN FACT, CREATE CONDITIONS SO YOU COULD -- YOU COULD CHILL IT AND STILL HAVE IT WORK AS A PCR REACTION, BUT YOU'D HAVE TO MANIPULATE ALL THE OTHER CONDITIONS IN ORDER TO TAKE THAT INTO ACCOUNT.

Q. DOCTOR, THE . . . POST-DOCTORAL STUDENTS WHO ARE WORKING WITH THIS REACTION WE'VE BEEN TALKING ABOUT OF MAKING A PROBE USING DOUBLE-STRANDED DNA --

A. UH-HUH.

Q. -- AND AN EXCESS OF PRIMERS --

A. UH-HUH.

Q. -- THEY WERE WORKING OUT THE CONDITIONS FOR THAT ON THEIR

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OWN?

A. OH, YES. OH, YES. THOSE WERE SUFFICIENTLY ROUTINE THAT THEY COULD GET IT OUT OF THE MANIATIS CLONING MANUAL; THEY COULD GET IT OUT -- WELL, BEFORE THAT EXISTED, THERE WERE WORK SHEETS AND ALL, YES.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) DOCTOR, IN YOUR OPINION, IF A POST-DOCTORAL STUDENT HAD THE BASIC PRINCIPLE OF PCR IN THE LATE 1970'S, COULD THAT STUDENT HAVE WORKED OUT THE CONDITIONS FOR DOING THE REACTION ON A DOUBLE-STRANDED DNA A HUNDRED-BASE PAIRS IN LENGTH?

A. THAT'S -- THAT'S AN INTERESTING QUESTION.

IF THEY HAD THE . . . I DON'T WANT TO USE TECHNICAL TERMS, BECAUSE I'M NOT A PATENT PERSON, BUT, TO MY MIND, THE INVENTIVE CONCEPT WAS THE TIME WINDOW, YES, BUT NOT WITH THE INFORMATION THAT WAS IN THE LITERATURE.

AND WHAT -- I STARTED TO SAY THIS BEFORE AND YOU STOPPED ME:

WHAT I SAID IN MY DEPOSITION, AS YOU KNOW, IS, I DID BELIEVE THAT IN 1984, A POST-DOC IN MY LAB WITH ORDINARY SKILL IN THE ART, IF WE HAD KNOWN THAT PCR WORKED, COULD HAVE WORKED IT OUT.

I HAVE CHANGED MY MIND ON THAT. IT TAKES AN INVENTIVE INPUT THAT IS REALLY EXTRAORDINARY. I THINK THAT WAS A STROKE OF GENIUS.

Q. OKAY. WELL, IN ANY EVENT, WHEN WE -- WHEN WE CHATTED DURING YOUR DEPOSITION IN NOVEMBER --

A. UH-HUH.

Q. -- YOU BELIEVED THAT, BASED ON THE LITERATURE AVAILABLE, A POST-DOC COULD HAVE DONE THAT WITH ROUTINE OPTIMIZATION.

A. YES, BECAUSE -- BECAUSE I MYSELF DIDN'T APPRECIATE WHAT THAT -- THAT TIME WINDOW MEANT.

Q. OKAY.

A. THAT'S RIGHT.

Q. AND --

A. I WOULD GUESS --

Q. -- PART --

A. SORRY.

Q. PART OF THIS PREPARATION THAT YOU REFERRED TO --

MR. PASAHOW: EXCUSE ME, YOUR HONOR. I THINK DR. ANDERSON WAS STILL ANSWERING WHEN --

THE COURT: DID YOU FINISH YOUR LAST ANSWER?

Q. (BY MR. FIGG) I'M SORRY IF I INTERRUPTED YOU, SIR.

A. ACTUALLY, I DIDN'T, BUT I'VE FORGOTTEN WHAT -- THE LAST THING I WAS SAYING. WHAT DID I SAY?

MR. FIGG: WELL, WHY DON'T WE LEAVE IT AT THAT, DR. ANDERSON?

THANK YOU VERY MUCH.

THE WITNESS: OKAY. THANKS.

THE COURT: OKAY. THANK YOU.

MR. PASAHOW?

MR. PASAHOW: YES, YOUR HONOR. JUST A FEW THINGS.

REDIRECT EXAMINATION

BY MR. PASAHOW:

Q. YOU WERE TALKING ABOUT THESE REACTIONS WITH DOUBLE-STRANDED DNA AND PRIMERS GOING THOUSANDS.

A. UH-HUH.

Q. NOW, IN THOSE SYSTEMS --

A. THOUSAND.

Q. A THOUSAND.

A. A THOUSAND, YES.

Q. IN THOSE SYSTEMS, WAS THERE ONE PRIMER OR TWO PRIMERS?

A. THOSE WERE ONE PRIMER. ONE REALLY WOULDN'T DO IT WITH TWO PRIMERS, BECAUSE YOU'D JUST SORT OF GET A TANGLED MESS IF YOU DID THAT, USING THOSE -- THOSE CONDITIONS.

Q. NOW, IF -- IF I COULD TAKE A PIECE THAT WERE 3,000 OF THESE BASES LONG, THESE A'S AND C'S AND G'S AND T'S, AND GET THE PRIMER TO GO A THOUSAND, COULD I TAKE A SHORT PIECE, SAY A HUNDRED BASES LONG, AND COUNT ON THE PRIMER GOING TO THE END OF THAT?

A. (SHAKING HEAD.)

THE PROBLEM IS EXACTLY THE SAME. IT DOESN'T MAKE ANY DIFFERENCE IF IT'S THAT LONG (INDICATING), OR IF IT'S A BASKETBALL PLAYER AND IT'S THAT LONG (INDICATING). IT TAKES A FINITE LENGTH OF TIME TO MAKE, AND IT TAKES A LOT SHORTER TO DO

THIS (INDICATING) OR DO THAT (INDICATING).

NO, IT DOESN'T MAKE ANY DIFFERENCE HOW LONG THE TEMPLATE IS.

Q. WHY IS THAT?

A. YOU WANT TO GO INTO THE DELTA-FREE ENERGIES AND ALL THAT?

Q. NO, I DON'T.

(LAUGHTER)

Q. (BY MR. PASAHOW) IS THERE ANY -- ISN'T THERE AN EXPLANATION THAT WE WOULD UNDERSTAND THAT YOU COULD PROVIDE?

A. OH, YEAH. BECAUSE -- BECAUSE . . . THAT'S ONE NICE THING ABOUT MR. FIGG'S VELCRO THING. I MEAN, WHAT YOU'RE TALKING ABOUT -- AND I THINK THIS WAS MENTIONED. YOU . . . YOU -- THE AFFINITY FOR COMING TOGETHER IS VERY STRONG. IT IS VERY STRONG. I MEAN, I'M -- WE LIVE BECAUSE OF THAT. I MEAN, THAT'S OUR DNA. THAT'S WHAT MAKES LIFE POSSIBLE.

AND SO THOSE STRANDS ARE SUPPOSED TO COME TOGETHER, AND EVERY CELL DIVISION, THEY COME APART AND THEY COME BACK TOGETHER. IT IS VERY EFFICIENT.

IT DOESN'T -- DNA DOESN'T WANT SOME TAQ POLYMERASE COMING ON AND RUNNING -- IT DOESN'T WANT THAT. THAT'S NOT -- THAT'S NOT NORMAL. THAT'S NOT NATURAL.

SO, YES, THE -- ALL THE -- YOU KNOW, ONE CAN GO INTO DELTA-FREE ENERGIES, BUT ALL OF THAT IS SIMPLY GIVING THE CALCULATIONS OF WHY, IN NATURE, IT DOES THIS.

IT STAYS TOGETHER. IT ONLY COMES APART DURING CELL

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DIVISION. IT'S NOT -- THESE STRANDS AREN'T SUPPOSED TO COME APART. NATURE DIDN'T MAKE IT THAT WAY. WE -- WE FORCE IT TO DO THAT, BUT THEY WANT TO COME BACK TOGETHER.

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

THE COURT: MR. FIGG.

RECROSS-EXAMINATION

BY MR. FIGG:

Q. DR. ANDERSON, DO YOU BELIEVE A -- IF AN ORDINARY POST-DOC HAD TRIED TO DO THIS EXPERIMENT IN 1984, THAT PERSON WOULD HAVE CHOSEN THE KLENOW ENZYME AS THE ENZYME TO CARRY OUT THE REACTION? THAT'S A REASONABLE ASSUMPTION; ISN'T IT?

A. YEAH, I THINK SO. YEAH.

Q. YEAH.

A. I THINK SO.

MR. PASAHOW: EXCUSE ME, YOUR HONOR. I THINK WE ARE BEYOND THE SCOPE OF THE REDIRECT.

MR. FIGG: WELL, WE CERTAINLY ARE NOT, YOUR HONOR. IF I CAN BE PERMITTED TO --

THE COURT: WE CERTAINLY ARE NOT?

MR. FIGG: WE ARE NOT.

THE COURT: THERE WASN'T MUCH ROOM FOR -- MUCH SCOPE GIVEN --

MR. FIGG: WELL, THERE WAS QUITE A BIT.

THE COURT: -- BY MR. PASAHOW.

WHERE IS THIS GOING?

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MR. FIGG: WELL, MY NEXT QUESTION MAY IDENTIFY THAT.

THE COURT: WELL, LET'S HEAR THE NEXT QUESTION, THEN.

Q. (BY MR. FIGG) DR. ANDERSON, IN THE REDIRECT EXAMINATION --

A. UH-HUH.

Q. -- YOU AGAIN REFERRED TO THE FACT THAT THE STRANDS ARE GOING TO COME TOGETHER AFTER THE ENZYME -- AFTER THE PRIMER ANNEALS AND AFTER THE ENZYME EXTENDS ITSELF ON THIS PRIMER-TEMPLATE COMPLEX. IS THAT WHAT YOU'RE SAYING?

A. NO. SEE, AGAIN, THIS IS -- THIS IS A THREE-DIMENSIONAL TAKING PLACE OVER TIME.

WHAT IS HAPPENING IS THAT TWO STRANDS, THEY COME APART. AS SOON AS YOU START TO COOL, BEFORE YOU CAN -- BEFORE YOU EVEN REACH THE TEMPERATURE THE PRIMERS OR ANYTHING CAN COME ON, THEY'RE ALREADY COMING BACK TOGETHER.

SO THAT IT MIGHT TOUCH HERE (INDICATING), IT MIGHT TOUCH THERE (INDICATING), IT MIGHT TOUCH UP THERE (INDICATING), BUT IT'S ALREADY COMING BACK TOGETHER. YOU DON'T GET THE PRIMER ON THE WAY YOU CAN DO IT ON, YOU KNOW, A PIECE OF PAPER. YOU SAY, HERE'S THE PRIMER. IT DOESN'T HAPPEN THAT WAY.

Q. WELL, DOCTOR --

A. SO YOU'VE GOT TO GET THIS OTHER STRAND COMPLETELY AWAY. YOU'VE GOT TO DO THIS TO IT. SO THIS IS ALL THAT EXISTS.

Q. WELL, DOCTOR, YOU TOLD ME THAT, IN THE EXPERIMENT YOU DID WITH THE -- MAKING THE PROBE --

A. UH-HUH.

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Q. -- THAT THE PRIMER DID ANNEAL TO THE TEMPLATE --

A. YES.

Q. -- AND --

A. I ASSUME YOU'RE NOT TALKING ABOUT THE DOUBLE-STRANDED.

Q. YES, I AM TALKING ABOUT THE DOUBLE-STRANDED.

A. OKAY. RIGHT. OKAY. YES.

NOW, WHAT HAPPENS THERE IS THAT -- IS THAT WHEN YOU DENATURE, SO IT'S ALL SORT OF HERE (INDICATING), AND THEN YOU QUIT COOL, IT'S ALL SORT OF (INDICATING) . . . SORT OF . . . TANGLED UP.

BUT YOU'RE TALKING ABOUT BILLIONS AND TRILLIONS OF MOLECULES. AND WHEN YOU ADD ENOUGH PRIMER, YOU WILL FIND STRETCHES WHERE YOU COULD GO ON OUT AND MAKE 500, EVEN A THOUSAND.

Q. UH-HUH.

A. BUT -- BUT THAT . . . THAT -- THE EFFICIENCY OF BEING ABLE TO GO FROM THE BEGINNING TO THE END IS ESSENTIALLY ZERO, UNLESS -- UNLESS YOU GET THAT SECOND STRAND OUT OF THERE. EVEN IF IT'S ONLY FOR A FEW SECONDS, YOU'VE GOT TO GET IT OUT OF THERE.

Q. IS WHAT YOU'RE SAYING, IS THAT THE PRIMER WILL ANNEAL UNDER THOSE SITUATIONS --

A. TO SOME OF THE MOLECULES, YES, SIR.

Q. THAT YOU USED FOR MAKING YOUR PROBES.

A. YES, YES, ABSOLUTELY. IT WILL -- IT WILL ANNEAL TO SOME,

YES.

Q. AND, OBVIOUSLY, THE ENZYME FINDS THAT COMPLEX AND EXTENDS ON THE PRIMER.

A. YES. IF YOU HAVE ANY EXTENSION, THEN THAT HAS TO HAVE HAPPENED, YES.

Q. YEAH. AND THE KLENOW ENZYME HAS THE ABILITY TO DISPLACE THAT OTHER TEMPLATE IF IT REANNEALS.

A. AH, NOW, THAT'S -- THAT'S --

Q. WELL, IS THAT TRUE OR IS THAT NOT TRUE?

A. WELL, IT DEPENDS ON THE CONDITIONS, AND ONE CAN CERTAINLY SET UP NOT ARTIFICIAL CONDITIONS BECAUSE ALL CONDITIONS ARE ARTIFICIAL, BUT CONDITIONS WHERE A KLENOW CAN -- CAN DEVELOP ENOUGH ENERGY TO DISPLACE SOMEWHAT. BUT NOT WHEN YOU'RE TALKING ABOUT TWO LONG STRANDS OF VELCRO THAT COME TOGETHER, NO, SIR.

Q. NOT TOO LONG STRANDS.

A. TWO, T-W-O, TOO, T-O-O. BOTH.

Q. I SEE.

A. THAT DOESN'T MAKE SENSE.

ANYWAY, TWO STRANDS WHICH ARE LONG SO THAT THE TOTAL ENERGY OF THAT -- THE AFFINITY OF THOSE TWO IS BEYOND WHAT KLENOW CAN SEPARATE.

Q. RIGHT. THE LONGER THE STRANDS ARE, THE MORE DIFFICULT IT MIGHT BE FOR KLENOW TO SEPARATE THEM.

A. RIGHT.

Q. BUT IF THEY'RE SHORT STRANDS, IT'S NOT UNREASONABLE TO

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EXPECT THAT KLENOW WILL DISPLACE THE STRANDS.

A. NO, NO. THE -- NO. IF THOSE STRANDS HAVE ALREADY STARTED TO -- TO COME TOGETHER, AND THAT'S -- THAT TAKES SECONDS TO MINUTES, KLENOW DOES NOT HAVE THE ABILITY, EXCEPT UNDER VERY, VERY SPECIFIC CONDITIONS, TO BE ABLE TO DISPLACE.

(PAUSE IN PROCEEDINGS)

Q. (BY MR. FIGG) THE ABILITY OF KLENOW TO DISPLACE STRANDS OR TO -- TO EXTEND AND DISPLACE A STRAND IN FRONT OF IT WAS KNOWN CERTAINLY IN 1984; WASN'T IT?

A. OH, YES, INDEED. YES, INDEED.

Q. AND PEOPLE HAD UNDERSTOOD -- PEOPLE LIKE -- WELL, DNA ENZYMOLOGISTS HAD STUDIED THE CONDITIONS UNDER WHICH THAT WOULD OCCUR.

A. YES.

Q. AND THEY'D PUBLISHED THOSE CONDITIONS.

A. OH, ABSOLUTELY. AND THE CONCLUSIONS OF THAT ARE THAT -- THAT -- THAT THE KLENOW, IN THE FORCE IT GENERATES AS IT MOVES DOWN THE TEMPLATE, CAN GENERATE A CERTAIN AMOUNT OF FORCE. BUT THAT IS NOWHERE NEAR THE AMOUNT TO ACTUALLY SEPARATE TWO -- TWO DOUBLE-STRANDED . . . THE TWO STRANDS OF A DOUBLE-STRANDED DNA.

Q. NOW, DOCTOR, BETWEEN THE TIME YOU'VE HAD YOUR DEPOSITION AND TODAY WHEN YOU'VE CHANGED YOUR MIND ON THESE POINTS --

A. UH-HUH.

Q. -- THAT WE TALKED ABOUT IN YOUR DEPOSITION, YOU'VE HAD A NUMBER OF MEETINGS WITH CETUS AND CETUS' LAWYERS, I PRESUME.

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A. JUST SINCE I GOT HERE ON SUNDAY, YES.

MR. FIGG: YEAH. OKAY. THANK YOU, DOCTOR.

THE WITNESS: RIGHT. THANK YOU.

THE COURT: MAY THIS WITNESS BE EXCUSED WITHOUT BEING SUBJECT TO BEING RECALLED?

MR. PASAHOW: YES, YOUR HONOR.

MR. FIGG: YES, YOUR HONOR.

THE COURT: THANK YOU, DR. ANDERSON.

THE WITNESS: THANK YOU.

THE COURT: YOU ARE EXCUSED.

THE WITNESS: THANK YOU.

(WITNESS EXCUSED)

MR. PASAHOW: EVERYONE WANTS TO LEAVE US.

(LAUGHTER)

MR. PASAHOW: OUR NEXT WITNESS IS DR. HENRY ERLICH.

THE COURT: OKAY. DO YOU THINK THAT THIS MIGHT -- MAYBE BEFORE -- YOU'RE GOING TO BE FAIRLY LENGTHY ON DIRECT?

MR. PASAHOW: YES, YOUR HONOR.

THE COURT: MAYBE WE OUGHT TO TAKE OUR RECESS NOW, AND THEN START WITH HIS DIRECT EXAMINATION.

MR. PASAHOW: OH, OF COURSE, YOUR HONOR.

THE COURT: OKAY. SO WE'LL TAKE ABOUT 10, 15 MINUTES. LADIES AND GENTLEMEN, WE'LL SEE YOU AT THE CLOSE OF THE RECESS.

(JURY EXCUSED)

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(OPEN COURT, JURY NOT PRESENT:)

MR. FIGG: YOUR HONOR?

THE COURT: YES.

MR. FIGG: IF I MAY MENTION ONE THING DURING THE BREAK.

MR. PASAHOW INFORMED ME THIS MORNING THAT THEY LAUDABLY, I THINK, ARE CUTTING DOWN ON THEIR CASE CONSIDERABLY, AND WE MAY GET TO A SITUATION --

THE COURT: DID HE TAKE YOU BY SURPRISE AS MUCH AS HE DID ME --

MR. FIGG: YES.

THE COURT: -- WHEN HE FINISHED UP AS QUICKLY WITH DR. ANDERSON?

MR. FIGG: NOT ONLY THAT, BUT HE GAVE ME A COUPLE MORE SURPRISES, WHICH IS THAT THE LAST TWO WITNESSES MAY NOT BE CALLED AT ALL.

THE COURT: I SEE.

MR. FIGG: THIS PUTS US IN A SITUATION WHERE OUR REBUTTAL WITNESS IS -- TO BE HONEST, WE STILL HAVEN'T FIRMLY DECIDED ON WHO THEY'RE GOING TO BE IN TOTO, BUT WE DO KNOW ONE THING: THEY'RE OUT OF TOWN AND THEY WEREN'T EXPECTING TO BE HERE TOMORROW.

SO I JUST WANT TO BASICALLY SERVE WARNING, I GUESS, THAT WE MAY BE IN A SITUATION TOMORROW, IF WE FINISH UP WITH DR. ERLICH, THAT WE WON'T HAVE A WITNESS TO GO ON TOMORROW.

THE COURT: YOU HAVE DR. KLUG'S DEPOSITION YOU'RE GOING

TO DO?

MR. PASAHOW: WE DO INTEND TO DO THAT, FOR CERTAIN, YOUR HONOR. AND HOW MUCH WE DO BEYOND THAT WILL DEPEND UPON WHAT HAPPENS THE REST OF TODAY.

WHAT WE DID IS, IT BECAME CLEAR TO SEVERAL PEOPLE WHO WERE WATCHING THAT THE JURY'S ATTENTION SPAN IS ENORMOUSLY DECREASING.

THE COURT: THEY WERE GETTING A LITTLE GLAZED YESTERDAY. WE WERE ALL GETTING A LITTLE GLAZED.

MR. PASAHOW: FOR UNDERSTANDABLE REASONS, YES, YOUR HONOR.

AND SO WE HAVE -- WE HAVE TRIED TO MAKE SURE THAT WE ARE DUPLICATING NOTHING AND DOING NOTHING UNNECESSARILY IN HOPES OF MAKING SURE WE GET DONE NO LATER THAN TOMORROW.

MR. FIGG: THAT'S FINE.

THE COURT: WELL --

MR. FIGG: MY ONLY POINT WAS --

THE COURT: YOU DON'T WANT THE JURY TO BE UPSET.

MR. FIGG: -- WE WANT SOME INDULGENCE --

THE COURT: YOU DON'T WANT THE JURY TO BE UPSET THAT WE CAN'T START RIGHT AWAY, SO I THINK YOU'D BETTER START WORKING ON --

MR. FIGG: YES. WELL, WE HAVE BEGUN GETTING WORKING ON IT, BUT GETTING PEOPLE HERE FOR TOMORROW WOULD BE DIFFICULT BECAUSE WE THOUGHT MR. PASAHOW WOULD BE GOING TO TUESDAY.

THE COURT: WELL, DO YOU HAVE ANYONE LOCALLY THAT YOU INTENDED TO CALL FOR --

MR. FIGG: WELL, WE PROBABLY WILL CALL DR. KORNBERG, BUT, AS I UNDERSTAND, DR. KORNBERG IS INVOLVED IN SOME SEMINARS OR ACTIVITIES THIS WEEK.

THE COURT: UH-HUH.

MR. FIGG: WE HAD TOLD HIM IT WOULD BE NEXT WEEK, SO -- WE TOLD EVERYBODY IT WOULD BE NEXT WEEK.

THE COURT: WELL, WHAT DO WE HAVE? TODAY IS WEDNESDAY IN ANY EVENT, AND WE'RE NOT IN SESSION ON FRIDAYS, SO . . .

MR. FIGG: NOR MONDAY, I BELIEVE.

THE COURT: THAT'S RIGHT. MONDAY IS A HOLIDAY. I KNOW THESE HOLIDAYS KEEP CREEPING IN.

MR. FIGG: IT SEEMS LIKE A HOLIDAY TIME OF THE YEAR.

THE COURT: WELL, LET'S SEE WHERE WE -- SEE IF YOU CAN LINE UP SOMEONE, IF IT'S NECESSARY TO DO THAT, FOR TOMORROW.

MR. FIGG: WELL, WE'LL TRY, BUT I THINK IT WILL BE QUITE DIFFICULT FOR US TO DO THAT --

THE COURT: OKAY.

MR. FIGG: -- BECAUSE, AS I SAY, WE WERE EXPECTING ALL OF THIS TO COME ABOUT NEXT WEEK.

THE COURT: GIVEN THAT, I KNOW WHAT THE JURY'S NEXT QUESTION IS GOING TO BE, NONETHELESS: WHAT IS THE BOTTOM LINE IN ALL OF THIS?

MR. FIGG: RIGHT.

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THE COURT: HOW LONG A REBUTTAL CASE DO YOU BELIEVE YOU'LL PUT ON?

MR. FIGG: WE'RE THINKING PROBABLY NO MORE THAN TWO -- TWO SESSIONS, TWO DAYS.

THE COURT: AND THEN WHAT? ONE DAY MAYBE?

MR. PASAHOW: I'M NOT SURE WHO THE TWO DAYS -- TWO DAYS OF WITNESSES ARE, SO I'M REALLY NOT IN A POSITION TO RESPOND.

MR. FIGG: WELL, I WILL CERTAINLY LET MR. PASAHOW KNOW THAT.

THE COURT: CAN WE BE SURE THAT WE WILL BE FINISHED UP BY NEXT THURSDAY? CAN WE DO THAT?

MR. FIGG: YES. WELL, I THINK --

THE COURT: BOTH SIDES?

MR. PASAHOW: WELL --

THE COURT: LET'S REALLY WORK ON THAT. IF THAT MEANS TIGHTENING YOURS UP SO THAT THEY'RE NOT, YOU KNOW, LEFT OUT OF HAND.

MR. FIGG: RIGHT.

MR. PASAHOW: IF WE FIND OUT WHO THE REBUTTAL WITNESSES WILL BE, WE CAN CERTAINLY WORK ON THAT.

MR. FIGG: OKAY.

THE COURT: OKAY.

MR. FIGG: WELL, WE STILL HAVE A FEW WITNESSES TO GO HERE, SO WE HAVEN'T FULLY DECIDED ON WHO THEY'RE GOING TO BE, EITHER.

THE COURT: OKAY. WELL, ONLY TWO APPARENTLY.

MR. FIGG: RIGHT.

THE COURT: IS THAT CORRECT?

(PAUSE IN PROCEEDINGS)

MR. FIGG: WE'LL SETTLE ON THAT.

THE COURT: WELL, YOU'LL NEED TO MAKE SOME DECISIONS THIS AFTERNOON ABOUT THAT.

MR. FIGG: RIGHT.

THE COURT: OKAY. FINE. ARE YOU GOING TO PROCEED WITH DR. ERLICH AND THEN FINISH UP WITH THE -- THE KLUG DEPOSITION?

MR. PASAHOW: IF MR. FIGG DOES NOT SPEND THE REST OF OUR TIME ON THE CROSS-EXAMINATION OF DR. ERLICH, YES, WE WILL GO TO --

THE COURT: HOW LONG ARE YOU GOING TO BE WITH DR. ERLICH ON DIRECT? AN HOUR?

MR. PASAHOW: IT TAKES A LITTLE BIT OVER AN HOUR --

THE COURT: OKAY.

MR. PASAHOW: -- I HOPE.

THE COURT: WE'LL SEE YOU AFTER THE RECESS THEN.

(RECESS TAKEN AT 9:40 A.M.)

(CONTINUED ON NEXT PAGE, NOTHING OMITTED)