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1 TUESDAY, FEBRUARY 5, 1991

8:15 A.M.

2  
3 (OPEN COURT, JURY PRESENT:)

4 THE COURT: GOOD MORNING.

5 THE WITNESS: GOOD MORNING.

6 THE COURT: HOW ARE YOU?

7 GOOD MORNING, LADIES AND GENTLEMEN.

8 THE JURORS: GOOD MORNING.

9 THE COURT: AND, COUNSEL, GOOD MORNING.

10 MR. FIGG: GOOD MORNING, YOUR HONOR.

11 MR. PASAHOW: SHALL I PROCEED, YOUR HONOR?

12 THE COURT: YOU MAY, YES.

13 MR. PASAHOW: MS. MORIYAMA POINTS OUT THAT THE FIRST  
14 THING WE SHOULD DO IS MARK THE DIAGRAM THAT DR. SMITH DREW FOR  
15 US YESTERDAY.

16 THE CLERK: DEFENDANT'S B-251 MARKED FOR IDENTIFICATION  
17 ONLY.

18 (DEFENDANT'S EXHIBIT B-251

19 MARKED FOR IDENTIFICATION)

20 MR. PASAHOW: THANK YOU.

21 HAMILTON OTHANEL SMITH, DEFENDANT'S WITNESS, PREVIOUSLY SWORN

22 RESUMED

23 DIRECT EXAMINATION RESUMED

24 BY MR. PASAHOW:

25 Q. GOOD MORNING, DR. SMITH.

1 A. GOOD MORNING.

2 Q. DR. SMITH, YOU ASKED THAT WE MAKE SURE SOMETHING IS CLEAR  
3 ABOUT THE TESTIMONY YOU GAVE ABOUT THE NOBEL PRIZE.

4 DID YOU RECEIVE THAT NOBEL PRIZE -- WERE YOU -- WHEN  
5 YOU RECEIVED THAT NOBEL PRIZE, WERE YOU THE ONLY PERSON WHO  
6 RECEIVED THE NOBEL PRIZE FOR MEDICINE THAT YEAR?

7 A. NO. I SHARED THE PRIZE WITH TWO OTHER SCIENTISTS, DR. ARBER  
8 (PHONETIC), WHO WAS A RESEARCHER IN SWITZERLAND, AND DR. DANIEL  
9 NATHANS, WHO WAS A CLOSE COLLEAGUE OF MINE, STILL IS A CLOSE  
10 COLLEAGUE OF MINE, AT JOHNS HOPKINS.

11 DR. ARBER -- WE EACH CONTRIBUTED DIFFERENTLY TO THE --  
12 TO THE WORK. DR. ARBER DID THE FUNDAMENTAL MOLECULAR BIOLOGY  
13 AND PREDICTED RESTRICTION ENZYMES; I ACTUALLY ISOLATED THE FIRST  
14 CLEAVAGE SITE-SPECIFIC RESTRICTION ENZYME; AND THEN DR. NATHANS  
15 USED MY ENZYME TO DO SOME FUNDAMENTAL -- SOME OF THE VERY FIRST  
16 APPLICATIONS OF RESTRICTION ENZYMES TO THE ANALYSIS OF SMALL  
17 VIRUSES.

18 Q. WELL, WITH THAT CLARIFICATION, ON B-251 --

19 COULD I ASK YOU TO COME DOWN AND REVIEW FOR US WHAT  
20 THIS IS:

21 (PAUSE IN PROCEEDINGS)

22 THE WITNESS: YES. THIS WAS A -- THE DRAWING OF THE  
23 PARTICULAR DNA GENE THAT DR. KHORANA'S GROUP WAS ATTEMPTING TO  
24 MAKE COPIES OF WHEN HE HAD CHEMICALLY SYNTHESIZED IT.

25 AND, AS HE POINTED OUT IN SEVERAL PLACES IN THE KLEPPE

1 ARTICLE, THIS PARTICULAR GENE HAS THE CAPABILITY, WHEN YOU  
2 SEPARATE THE TWO DNA STRANDS, FOR EACH OF THE STRANDS TO FOLD  
3 INTO A -- WHAT HE CALLED A CLOVERLEAF STRUCTURE -- THIS WAS WELL  
4 KNOWN, ACTUALLY -- IN WHICH THERE IS BASE PAIRING IN EACH OF  
5 THESE SO-CALLED STEMS. THESE ARE STEM-LOOP STRUCTURES.

6 AND HE SPECULATED IN THE -- IN -- KLEPPE IN THE  
7 ARTICLE -- IN THE KLEPPE ARTICLE, SPECULATED THAT THERE COULD BE  
8 PROBLEMS IN TERMS OF OBTAINING THE APPROPRIATE FULL-LENGTH  
9 PRODUCTS, AND I WANTED TO POINT THAT OUT TO THE JURY.

10 WHAT HAPPENS IS THAT IF YOU PRIME -- FOR EXAMPLE, WE  
11 ASSUME THAT THE MOLECULES, WHEN THEY FORM THESE STRUCTURES, SOME  
12 OF THE MOLECULES MAY FORM PERFECT CLOVERLEAFS AND SOME OTHERS  
13 MAY FORM PARTIAL CLOVERLEAFS WITH ONE OR TWO LOOPS --  
14 STEM-LOOPS.

15 SOME OF THESE MOLECULES CAN BE PRIMED EFFECTIVELY, AND  
16 SO HERE WOULD BE THE PRIMER ANNEALED TO THE MOLECULE, AND THEN  
17 POLYMERIZATION WOULD LEAD TO EXTENSION AND, BY A PROCESS WHICH  
18 IS ANALOGOUS TO WHAT'S COMMONLY REFERRED TO AS STRAND SWITCHING,  
19 ONE CAN LITERALLY SKIP OVER THE BASE OF THIS STEM-LOOP STRUCTURE  
20 TO THE OTHER SIDE AND ESSENTIALLY DELETE THIS WHOLE PORTION OF  
21 THE -- OF THE COPY.

22 SO THAT INSTEAD OF COPYING ALL THE WAY AROUND LIKE  
23 THIS, TO FORM A COMPLETE COPY, YOU FORM A SHORT COPY WHERE YOU  
24 SIMPLY SKIP THESE REGIONS HERE.

25 THE OTHER POSSIBLE TYPE OF PRODUCT WOULD BE ONE WHERE

1 YOU SIMPLY GO UP TO THE FIRST OR THE SECOND STEM AND THE  
2 POLYMERASE WOULD HAVE DIFFICULTY GOING PAST THAT POINT, AND YOU  
3 WOULD FORM A SHORT PRODUCT.

4 SO THERE ARE TWO TYPES OF PRODUCTS HERE, NEITHER ONE OF  
5 WHICH IS TYPICALLY FULL-LENGTH COPIES OF THE GENE.

6 Q. (BY MR. PASAHOW) NOW, IF WE GOT WHAT YOU REFERRED TO AS THE  
7 SHORT PRODUCT, WHERE IT GOES UP TO ONE OF THE LOOPS AND STOPS,  
8 WHAT WOULD HAPPEN IF YOU TRIED TO USE THAT PRODUCT IN ANOTHER  
9 CYCLE AS A TEMPLATE TO TRY AND MAKE THE REVERSE COMPLEMENTARY  
10 STRAND?

11 A. WELL -- YES. IT WOULDN'T. SINCE THE OTHER PRIMER IS  
12 COMPLEMENTARY TO THE FAR END, AND YOU NEVER REACH THAT POINT,  
13 IT'S OBVIOUS THAT YOU -- THAT THIS SHORT COPY WOULD NOT TAKE --  
14 WOULD NOT BE INVOLVED IN THE NEXT CYCLE OF REACTION. IT COULD  
15 NOT SERVE AS A TEMPLATE IN THE NEXT CYCLE.

16 Q. AND SUPPOSE YOU GOT THE OTHER ALTERNATIVE WHERE IT SKIPPED  
17 OVER SOME OF THE LOOPS.

18 A. RIGHT. IF YOU FORM A SHORT PRODUCT, YOU NOW INDEED HAVE THE  
19 COMPLEMENTARY REGION FOR THE PRIMING IN THE SECOND CYCLE, BUT  
20 YOU DON'T HAVE THE FULL-LENGTH STRUCTURE. SO YOU'RE NO LONGER  
21 FORMING -- YOU'RE NOT PRODUCING A COPY WHICH IS A FULL-LENGTH  
22 COPY OF THE ORIGINAL GENE.

23 Q. WHAT WOULD BE THE DIFFERENCE BETWEEN THE COPY YOU MADE AND  
24 THE ORIGINAL GENE?

25 A. WELL, THE COPY WOULD BE MUCH SHORTER. IT WOULD BE MISSING A

1 NUMBER OF SEQUENCES IN THE -- THE BASES WITHIN THE INTERNAL PART  
2 OF THE SEQUENCE.

3 Q. THANK YOU.

4 A. (WITNESS RESUMES WITNESS STAND.)

5 (PAUSE IN PROCEEDINGS)

6 Q. (BY MR. PASAHOW) NOW, WE WERE TALKING ABOUT THIS LAST  
7 PARAGRAPH IN KLEPPE, AND I THINK WE HAD GOTTEN TO THE POINT  
8 WHERE WE HAD READ:

9 "IF THIS TENDENCY COULD NOT BE CIRCUMVENTED  
10 BY ADJUSTING THE CONCENTRATIONS OF PRIMERS, CLEARLY  
11 ONE WOULD HAVE TO RESORT TO THE SEPARATION OF THE  
12 STRANDS AND THEN CARRY OUT REPAIR REPLICATION. AFTER  
13 EVERY CYCLE OF REPAIR REPLICATION, THE PROCESS OF  
14 STRAND SEPARATION WOULD HAVE TO BE REPEATED."

15 , WHAT DO -- WHAT DO THOSE TWO SENTENCES REFER TO?

16 A. WELL, WHAT THEY'RE SAYING IS THAT IF . . . ESSENTIALLY, IF  
17 YOU'RE HAVING A PROBLEM WITH THE RE-ANNEALING OF THE TEMPLATE  
18 STRANDS IN THE FIRST PROCEDURE, YOU WOULD HAVE TO SWITCH TO A --  
19 AN ENTIRELY DIFFERENT APPROACH, THE SECOND APPROACH WHICH HE  
20 DESCRIBES HERE, IN WHICH YOU DON'T HAVE BOTH STRANDS IN THE SAME  
21 TEST TUBE DURING THE REACTION.

22 YOU SEPARATE THE TWO STRANDS OF THE GENE AND PUT THEM  
23 INTO SEPARATE TUBES. THEN YOU MAKE A COPY OF -- THEN YOU PRIME  
24 AND EXTEND EACH OF THOSE TO MAKE A COMPLEMENTARY COPY. AND THEN  
25 EACH OF THOSE WOULD HAVE TO BE SEPARATED INTO SEPARATE TUBES AND

1 YOU WOULD REPEAT AGAIN THE SAME CYCLE.

2 SO IT WOULD INVOLVE A PHYSICAL SEPARATION OF THE  
3 STRANDS SO THAT THEY'RE NOT PRESENT IN THE SAME TUBE AT THE SAME  
4 TIME.

5 Q. AND THEN FINALLY THE PARAGRAPH SAYS:

6 "EXPERIMENTS BASED ON THESE LINES OF THOUGHT  
7 ARE IN PROGRESS."

8 CAN YOU TELL FROM THAT WHICH OF THE TWO PROCESSES DR.  
9 KHORANA'S LAB WAS EXPERIMENTING WITH?

10 A. NO, NOT PRECISELY. IT'S A VAGUE STATEMENT.

11 WHEN I ORIGINALLY READ THE PARAGRAPH, I INFERRED IT TO  
12 MEAN THAT HE WAS TALKING ABOUT THE SECOND PROCESS, BUT I THINK  
13 IT COULD BE EITHER ONE.

14 Q. NOW, WHAT DO YOU UNDERSTAND TO BE THE GOAL THAT THE KHORANA  
15 LAB WAS TRYING TO ACHIEVE THROUGH ONE OF THESE TWO PROCESSES?

16 A. WELL, THEY STATE IT VERY CLEARLY THERE. THEY WILL -- VERY  
17 SHORTLY AFTER THIS PAPER WAS PUBLISHED, THEY WILL HAVE HAD THE  
18 ENTIRE TRNA GENE SYNTHESIZED, AND -- BUT THEY'LL ONLY HAVE A  
19 VERY SMALL AMOUNT OF IT, PERHAPS ONLY A FEW MICROGRAMS.

20 AND THE GOAL WAS TO THEN, INSTEAD OF GOING THROUGH THE  
21 VERY ARDUOUS RESYNTHESIS ORGANICALLY, TO SUBSTITUTE A VERY -- A  
22 MUCH SIMPLER ENZYMATIC APPROACH TO MANUFACTURE MORE OF THIS  
23 PRECIOUS SEQUENCE.

24 AND SO, IN EFFECT, THEY WANT TO HAVE AN EFFICIENT WAY  
25 TO COPY OR TO MANUFACTURE MORE OF THE PRODUCT -- OF THE GENE.

2 1 Q. DO YOU HAVE AN OPINION AS TO WHETHER THAT PARTICULAR GOAL  
2 WOULD HAVE AN EFFECT ON THEIR ABILITY TO SUCCESSFULLY COME UP  
3 WITH CONDITIONS UNDER WHICH PCR WOULD WORK?

4 A. I THINK IT STEERED THEM IN THE WRONG DIRECTION, BECAUSE IF  
5 YOU WANT TO MANUFACTURE QUANTITIES OF A -- A GENE BY THE SCHEMES  
6 THAT THEY OUTLINE HERE, YOU WOULD TEND TO START WITH A  
7 REASONABLE AMOUNT OF MATERIAL IN YOUR REACTION. LET'S SAY, FOR  
8 EXAMPLE, A MICROGRAM IN A REACTION. AND AFTER ONE CYCLE, YOU --  
9 IF YOU -- IF EVERYTHING WENT WELL, YOU COULD PRODUCE THEN TWO  
10 MICROGRAMS.

11 HOWEVER, IF YOU WERE TO EMPLOY THE CONDITIONS OF PC --  
12 THAT ARE COMMON IN PCR, NAMELY, A HUNDRED- TO EVEN A  
13 MILLION-FOLD LESS TEMPLATE, IN EFFECT . . . LET'S SUPPOSE THAT  
14 THEY USED A HUNDREDTH OF A MICROGRAM RATHER THAN ONE MICROGRAM,  
15 THEN THE FIRST CYCLE WOULD GIVE YOU TWO HUNDREDTHS OF A  
16 MICROGRAM, NOT A USEFUL AMOUNT. IN FACT, YOU WOULD HAVE TO RUN  
17 A NUMBER OF CYCLES TO GET A USEFUL AMOUNT OUT OF IT.

18 SO THE TENDENCY HERE WAS CLEARLY IN THE DIRECTION TO  
19 HAVE A LARGE AMOUNT OF TEMPLATE PRESENT EARLY IN THE REACTION.

20 Q. IN PCR, WHAT IS THE EFFECT IF YOU USE A LARGE AMOUNT OF  
21 TEMPLATE?

22 A. WELL, YOU HAVE A POOR REACTION. ALMOST ALL PCR REACTIONS  
23 ARE DONE WITH MINISCULE AMOUNTS OF DNA, COMPLETELY DIFFERENT  
24 FROM THE OBJECTIVE THEY WERE TRYING TO ACCOMPLISH HERE. PCR IS  
25 PRIMARILY A DETECTION LEVEL METHOD.

2  
1 Q. WHY ARE THE PCR REACTIONS DONE WITH A MINISCULE AMOUNT OF  
2 TEMPLATE?

3 A. WELL, BECAUSE YOU DON'T HAVE THE PROBLEM OF TEMPLATE  
4 ANNEALING WITH ITSELF.

5 Q. NOW, DR. KORNBERG TOLD US WHEN HE TESTIFIED THAT THIS  
6 PARTICULAR PARAGRAPH IS IN SOMETHING CALLED THE DISCUSSION  
7 SECTION OF THE ARTICLE; IS THAT RIGHT?

8 A. THAT'S RIGHT.

9 Q. AND DR. KORNBERG TOLD US THAT WHEN WORK APPEARS IN A  
10 DISCUSSION SECTION IN THIS WAY, THAT AFTER THE WORK IS DONE, IF  
11 IT'S SUCCESSFUL, IT'S USUALLY PUBLISHED IN ITS OWN DETAILED  
12 ARTICLE.

13 HAVE YOU OBSERVED THAT AS WELL?

14 A. YES. IF THEY HAD ACTUALLY ACCOMPLISHED SUCCESSFUL  
15 EXPERIMENTS, YOU WOULD EXPECT THEM TO PUBLISH A PAPER WHICH  
16 DESCRIBED THOSE EXPERIMENTS AND ACTUALLY GAVE DATA.

17 Q. IS THERE AN EXPERIMENT -- I'M SORRY.

18 IS THERE AN ARTICLE IN WHICH DR. KHORANA'S LABORATORY  
19 DID PUBLISH EXPERIMENTS AND GIVE DATA ABOUT ONE OF THE TWO  
20 PROPOSALS THAT ARE SET FORTH IN THIS PARAGRAPH?

21 A. YES, I KNOW OF ONE -- ONE PAPER.

22 Q. WHAT PAPER IS THAT?

23 A. THAT IS THE PAPER BY PANET AND KHORANA, I THINK PUBLISHED IN  
24 1974. I DON'T HAVE A COPY OF IT HERE.

25 Q. LET ME HAND YOU A COPY. WE'VE MARKED IT AS EXHIBIT A-1 --

3  
1 I'M SORRY -- A-19.

2 A. UH-HUH.

3 Q. IS THAT THE ARTICLE THAT YOU WERE REFERRING TO?

4 A. YES, THAT'S IT.

5 Q. NOW, WHICH OF THE TWO PROPOSALS IN THE PARAGRAPH HERE IN  
6 KLEPPE IS THE SUBJECT OF THAT ARTICLE?

7 A. THIS ARTICLE DEALS WITH THE SECOND PROPOSAL.

8 Q. HOW CAN YOU TELL THAT?

9 A. WELL, THE ARTICLE DESCRIBES REACTIONS WITH ONLY ONE STRAND  
10 RATHER THAN TWO. IT'S -- AND IT DESCRIBES HOW THEY ATTACHED ONE  
11 STRAND, NAMELY, THE TEMPLATE STRAND, TO A PARTICLE -- TO  
12 PARTICLES OF CELLULOSE, AND THEN THEY PRIMED -- ADDED PRIMER AND  
13 ANNEALED IT TO THAT SINGLE STRAND AND EXTENDED.

14 AND THEN IN THE NEXT STEP, THEY MELT OFF THE  
15 NEWLY-SYNTHESED STRAND AND THEN SIMPLY, BY GENTLE  
16 CENTRIFUGATION, WERE ABLE TO BRING THE TEMPLATE STRAND WHICH IS  
17 BOUND TO THE PARTICLES OF CELLULOSE DOWN TO THE BOTTOM OF THE  
18 TEST TUBE, WHEREAS THE PRODUCT REMAINS IN THE SOLUTION UP ABOVE.

19 AND SO THEY CAN THEN REMOVE THOSE TWO FRACTIONS, AND  
20 THEY'VE SEPARATED THE TEMPLATE FROM THE -- THE PRODUCT STRAND,  
21 AND THEY CAN NOW PUT THOSE IN SEPARATE TEST TUBES AND PROCEED  
22 WITH ANOTHER ROUND OF SYNTHESIS.

23 SO THAT'S DESCRIBED IN THIS PAPER.

24 Q. NOW --

25 A. AND THAT'S CLEARLY THE SECOND METHOD.

3  
1 Q. GOING BACK TO THE 1984 ORDINARILY-SKILLED POST-DOCTORAL  
2 FELLOW, WHAT WOULD SHE OR HE CONCLUDE FROM THE KHORANA LABS,  
3 GOING TO THE SECOND OF THE TWO PROPOSALS THAT ARE EXPLAINED IN  
4 THE LAST PARAGRAPH OF THE KLEPPE ARTICLE?

5 A. I THINK IT WOULD BE A STRAIGHTFORWARD CONCLUSION THAT THE  
6 FIRST METHOD DID NOT WORK, BECAUSE IN THE LAST PARAGRAPH OF  
7 KLEPPE, THE STATEMENT IS MADE THAT IF THE FIRST METHOD DIDN'T  
8 WORK, THEY WOULD HAVE TO TRY THE SECOND METHOD. THAT'S WHAT  
9 THEY'VE DONE.

10 Q. NOW, THERE HAS BEEN TESTIMONY ABOUT A PARTICULAR PARAGRAPH,  
11 OR AT LEAST A PORTION OF A PARAGRAPH FROM THIS PANET ARTICLE.

12 WE'VE GOT A POSTER OF THAT. I'LL SHOW IT TO YOU. IT'S  
13 B-173.

14 ARE YOU FAMILIAR WITH THAT PORTION OF THAT PARAGRAPH?

15 A. YES, I'VE READ THAT.

16 Q. HOW DO YOU INTERPRET WHAT IT SAYS?

17 A. WELL, AGAIN, THEY DESCRIBE, ESSENTIALLY AS THEY DID IN THE  
18 KLEPPE PAPER, THE STEPS OF THE PROCEDURE. AND AFTER DESCRIBING  
19 IT, THEY . . . CONCLUDE WITH THE STATEMENT SAYING THAT:

20 "THERE WAS SEVERE LIMITATION ON THE EXTENT OF  
21 NET SYNTHESIS THAT COULD BE ACHIEVED IN THE ABOVE  
22 APPROACH AND THE WORK DESCRIBED HEREIN WAS, THEREFORE,  
23 UNDERTAKEN."

24 SO THEY'RE EXPLAINING ESSENTIALLY THAT THAT PROCEDURE  
25 DID NOT WORK, THERE WAS VERY LITTLE SYNTHESIS, AND THAT NOW THEY

3 1 GO TO THIS OTHER METHOD, WHICH THEY ACTUALLY HAVE DATA FOR.

2 THEY EXPLAINED THE METHOD; THEY PRODUCED THE DATA. IT'S CLEAR  
3 WHAT THEY'RE DOING.

4 Q. WHICH METHOD DID THEY PROVIDE DATA FOR?

5 A. THIS IS THE SECOND METHOD, WHERE YOU ISOLATE STRANDS. AND  
6 IT'S NOT A PCR-TYPE PROCEDURE OR PROCESS.

7 Q. HOW -- HOW DO YOU BELIEVE THE 1984 ORDINARILY-SKILLED  
8 POST-DOCTORAL CANDIDATE WOULD REACT TO -- TO THIS PARAGRAPH IF  
9 HE WERE READING THROUGH THE SERIES OF KHORANA LABORATORY PAPERS?

10 A. WELL, I THINK HE WOULD BE DISCOURAGED FROM TRYING THE  
11 SECOND -- THE FIRST PROCEDURE THAT WAS DESCRIBED IN KLEPPE.

12 Q. WHY?

13 A. BECAUSE, CLEARLY, THE KHORANA LAB HAS ABANDONED THAT  
14 PROCEDURE AND GONE ON TO THE SECOND ONE.

15 Q. NOW, DOES THIS PARAGRAPH EXPLAIN HOW LONG THE PRIMERS WERE  
16 THAT WERE -- THAT WERE USED IN THIS UNPUBLISHED WORK BY DR.  
17 MOLINEUX?

18 A. NO, IT DOESN'T.

19 Q. DOES THE ARTICLE EXPLAIN WHAT THE PRODUCT WAS OF -- OF  
20 WHATEVER REACTION HE WAS ABLE TO RUN?

21 A. NO, IT DOESN'T. IT -- IT ONLY COMMENTS THAT THERE WAS  
22 SEVERE LIMITATION ON THE AMOUNT OF SYNTHESIS. IT DOESN'T  
23 DESCRIBE THE PRODUCT.

24 Q. DOES THE PARAGRAPH EXPLAIN HOW MUCH OF THE PRODUCT WAS MADE?

25 A. IT DOESN'T SAY PRECISELY HOW MUCH WAS MADE, NO.

3 1 Q. NOW, THIS IS THIS PHRASE THAT WE'VE HEARD TESTIMONY ABOUT,  
2 "AN EXCESS OF 10 TIMES OR MORE OF THE APPROPRIATE PRIMERS."

3 HOW DO YOU BELIEVE THE ORDINARILY-SKILLED 1984  
4 POST-DOCTORAL FELLOW WOULD INTERPRET THE PHRASE "AN EXCESS OF 10  
5 TIMES OR MORE"?

6 A. WELL, YOU'RE REFERRING TO 10 TIMES OR MORE MOLECULES OF  
7 PRIMER THAN NUMBER OF TEMPLATE STRANDS.

8 "10 TIMES OR MORE" IS SOMEWHAT INDEFINITE, BUT THE 1984  
9 POST-DOCTORAL FELLOW WOULD PROBABLY DRAW ON HIS EXPERIENCE WITH  
10 SEQUENCING AND OTHER METHODS TO CONCLUDE THAT THAT MIGHT MEAN 20  
11 TIMES OR POSSIBLY 30 TIMES.

12 (PAUSE IN PROCEEDINGS)

13 Q. (BY MR. PASAHOW) AND WHAT WOULD THE ORDINARILY-SKILLED  
14 POST-DOC IN 1984 CONCLUDE ABOUT THE PHRASE "APPROPRIATE  
15 PRIMERS"? WHAT WOULD HE BELIEVE THE APPROPRIATE PRIMERS WERE?

16 A. WELL, I THINK HE COULD INFER THAT THOSE WOULD BE PRIMERS  
17 THAT ARE SITUATED AT THE TWO ENDS OF THE GENE.

18 Q. WOULD HE KNOW THE LENGTH THAT DR. MOLINEUX HAD USED IN HIS  
19 WORK?

20 A. NO. IT'S NOT STATED HERE. IT COULD BE A LENGTH -- I THINK  
21 WE COVERED THAT IN TESTIMONY YESTERDAY. IT COULD BE A LENGTH  
22 GOING FROM PERHAPS FIVE UP TO 20 OR SO.

23 Q. NOW, THIS -- THIS ARTICLE THAT -- BY DR. PANET AND KHORANA  
24 WAS PUBLISHED IN 19 -- AUGUST 1974; IS THAT RIGHT?

25 A. THAT'S RIGHT.

4 1 Q. NOW, I'D LIKE TO SHOW YOU ANOTHER PAPER WHICH WAS PUBLISHED  
2 IN 1975 FROM THE KHORANA LABORATORY. IT WAS TO THE NATIONAL  
3 CANCER INSTITUTE, OR THE NATIONAL INSTITUTE OF HEALTH.

4 WE'VE MARKED IT AT EXHIBIT B-159.

5 MR. PASAHOW: AND I SHOULD INDICATE THAT THIS IS THE --  
6 I BELIEVE, THE LAST OF THE ITEMS IN THE JURY BOOKS THAT WERE  
7 PROVIDED TO THE JURY.

8 Q. ARE YOU FAMILIAR WITH AT LEAST PORTIONS OF THIS GRANT  
9 PROPOSAL?

10 A. YES.

11 Q. AND I -- YOU'VE FOCUSED YOUR ATTENTION ON A PARTICULAR  
12 PARAGRAPH; IS THAT RIGHT?

13 A. YES, WE DID.

14 Q. AND THAT PARAGRAPH IS FROM PAGE 39, WHERE DR. KHORANA HAS  
15 THIS PARAGRAPH ENTITLED, "THE REPLICATION OF SYNTHETIC LINEAR  
16 DOUBLE-STRANDED DNA"?

17 A. YES.

18 Q. COULD YOU PLEASE EXPLAIN FOR US WHAT THE PARAGRAPH SAYS.

19 A. IT'S -- I SHOULD POINT OUT, IT'S IN THE FINAL PROGRESS  
20 REPORT OF THE FIVE-YEAR -- OF THE FIVE-YEAR GRANT THAT PRECEDED  
21 THIS ONE, GRANT APPLICATION.

22 AND IT AGAIN DESCRIBES VERY BRIEFLY THE PROCESS THAT  
23 WAS DESCRIBED IN THE FIRST PART OF THAT PARAGRAPH OF THE KLEPPE  
24 REPORT, AND IT CONCLUDES WITH THE STATEMENT THAT:

25 "ALTHOUGH LIMITED SYNTHESIS (TWO TO THREE

4 1            ROUNDS) COULD BE ACHIEVED, EXTENSIVE AND COMPLETE  
2            REPLICATION OF THE STARTING DNA COULD NOT BE  
3            REALIZED."

4            AND SO HE'S SAYING THAT THEY COULD NOT -- THEY COULD  
5 NOT REALIZE AN EXTENSIVE REPLICATION, WHATEVER THAT MEANS. IT'S  
6 NOT CLEAR.

7            BUT THE MOST IMPORTANT THING IS THAT THEY COULD NOT  
8 REALIZE COMPLETE REPLICATION OF THE STARTING DNA.

9 Q.    WHY IS THAT IMPORTANT?

10 A.    THAT SIMPLY MEANS THAT THEY WERE UNABLE TO GET FULL-LENGTH  
11 COPIES OF THE MOLECULE. THEY COULD NOT REALIZE COMPLETE  
12 REPLICATION OF THE STARTING DNA.

13            IF THE STARTING DNA WAS THIS LONG (INDICATING), HE'S  
14 SAYING THAT THEY'RE INCOMPLETE. HE'S GETTING PORTIONS OF THE  
15 TEMPLATE COPIED BUT NOT THE ENTIRE MOLECULE.

16 Q.    AND JUST SO IT'S VERY CLEAR, COULD YOU EXPLAIN FOR US WHY IT  
17 MATTERS WHETHER THE COPIES ARE COMPLETE.

18 A.    WELL, AGAIN, THE . . . IF THE MOLECULE -- IF THE TEMPLATE IS  
19 NOT COMPLETELY COPIED, THEN . . . PARTICULARLY IF THE FAR END OF  
20 THE . . . NEWLY-SYNTHEZIZED STRAND IS NOT COMPLETED, YOU DON'T  
21 HAVE THE SITE FOR THE PRIMER. THIS STRAND CANNOT ACT AS A  
22 TEMPLATE IN THE NEXT CYCLE BECAUSE THERE'S NO SITE FOR THE NEXT  
23 PRIMER TO BIND TO AT THAT END.

24 Q.    NOW, IF THE 1984 ORDINARILY-SKILLED POST-DOC WERE GOING  
25 THROUGH THE SERIES OF PAPERS FROM THE KHORANA LAB AND READ THIS,

4 1 WOULD THAT HAVE AN INFLUENCE ON HIS TRYING THE METHOD THAT'S  
2 DESCRIBED IN THE KLEPPE PAPER?

3 A. WELL, IT'S A VERY CLEAR STATEMENT FROM DR. KHORANA HIMSELF  
4 THAT THE METHOD DOES NOT WORK, AND . . . HE HAS ONE OF THE BEST  
5 LABORATORIES IN THE COUNTRY. I THINK THE ORDINARY POST-DOC  
6 WOULD BE VERY DISCOURAGED BY THAT STATEMENT.

7 Q. NOW, THERE'S ONE OTHER GRANT PROPOSAL THAT WE'VE BEEN  
8 LOOKING AT. THIS ONE IS THE NATIONAL CANCER INSTITUTE -- THE  
9 ONE WE JUST LOOKED AT IS THIS NATIONAL CANCER INSTITUTE ONE IN  
10 1975.

11 AND THERE'S AN EARLIER ONE BACK IN OCTOBER 1972 HERE  
12 THAT WE'VE BEEN LOOKING AT, AND THAT IS EXHIBIT A-17.

13 (PAUSE IN PROCEEDINGS)

14 Q. (BY MR. PASAHOW) LET ME SHOW YOU THAT.

15 HAVE YOU SEEN IT BEFORE?

16 A. YES, I HAVE.

17 Q. NOW, AGAIN, WE'VE FOCUSED ON A PARTICULAR SECTION OF THAT  
18 DOCUMENT, AND THAT SECTION IS REPRODUCED HERE IN EXHIBIT B-174.

19 ARE YOU FAMILIAR WITH THAT SECTION?

20 A. YES. I'M TRYING TO FIND IT IN THE COPY I HAVE HERE.

21 HERE IT IS.

22 Q. IT'S ON PAGE 17 AND 18.

23 A. YES.

24 (PAUSE IN PROCEEDINGS)

25 Q. (BY MR. PASAHOW) NOW, STARTING WITH THE THREE NUMBERED

4 1 ITEMS JUST ABOVE THE DIAGRAM WHERE IT SAYS THERE'S A METHOD  
2 INVOLVING THE FOLLOWING STEPS, DO THOSE THREE STEPS DESCRIBE THE  
3 INVENTION THAT'S DESCRIBED IN CLAIM 1 OF THE '202 PATENT?

4 A. NOT IN MY OPINION. THEY ARE -- AGAIN, IT'S ESSENTIALLY THE  
5 SAME DESCRIPTION AS IN THE KLEPPE PAPER.

6 THERE'S A CERTAIN AMOUNT OF VAGUENESS IN IT. AND THE  
7 CRUCIAL FEATURE OF THE CLAIM 1 IS NOT HERE; NAMELY, THAT THE  
8 PRODUCTS OF ONE CYCLE CAN ACT AS TEMPLATE IN SUBSEQUENT CYCLES,  
9 OR IN THE NEXT CYCLE.

10 (PAUSE IN PROCEEDINGS)

11 Q. (BY MR. PASAHOW) NOW, JUST BELOW THAT, THERE IS THIS  
12 DIAGRAM WHERE IT SAYS STEP 1, STEP 2, AND HAS SOME PICTURES.

13 DO THOSE -- DO THOSE -- DOES THAT -- DO THOSE PICTURES  
14 IN THAT DIAGRAM SET OUT WHAT IS CLAIM 1 OF THE '202 PATENT?

15 A. NO, THEY DON'T. THEY'RE ESSENTIALLY THE SAME AS THE  
16 STATEMENTS ABOVE. IT'S AN ILLUSTRATION OF THAT.

17 Q. LOOKING AT THIS DIAGRAM, ARE YOU ABLE TO TELL WHAT THE  
18 LENGTH IS OF THE PRIMERS THAT ARE INDICATED BY THESE TWO LITTLE  
19 LINES BETWEEN THE FIVE-PRIME AND THE THREE-PRIME HERE  
20 (INDICATING) AND HERE (INDICATING)?

21 A. WELL, THERE'S NO SCALE ON THE DIAGRAM, SO IT WOULD BE VERY  
22 DIFFICULT TO -- TO TELL.

23 Q. HAVE YOU EVER SERVED ON GRANT COMMITTEES FOR THE NATIONAL  
24 SCIENCE FOUNDATION?

25 A. YES, I HAVE.

5 1 Q. NOW, DO YOU SEE THE LANGUAGE IN THIS PARAGRAPH TOWARDS THE  
2 END WHERE DR. KHORANA WROTE THAT THERE WERE EXPERIMENTS IN HIS  
3 LABORATORY AND THAT THE RESULTS -- THE PRELIMINARY RESULTS ARE  
4 ENCOURAGING?

5 A. I SEE THAT, YES.

6 Q. IN YOUR EXPERIENCE AS A REVIEWER ON NATIONAL SCIENCE  
7 FOUNDATION GRANT REVIEW PANELS, HOW WOULD YOU INTERPRET THAT  
8 LANGUAGE?

9 A. I WOULD INTERPRET IT TO MEAN THAT THEY STILL DON'T HAVE ANY  
10 CLEAR-CUT DATA WHICH RULES OUT THIS METHOD, BUT NEITHER DO THEY  
11 HAVE DATA THAT CONFIRMS IT.

12 Q. WOULD YOU TAKE THAT TO MEAN THAT THEY HAD ALREADY  
13 SUCCESSFULLY PERFORMED THE PROCESS THAT'S DESCRIBED?

14 A. NO, I -- I THINK THAT IF THEY HAD THE PROCESS GOING, THEY  
15 WOULD HAVE GIVEN SOME PILOT STUDY DATA TO SUPPORT THEIR -- THEIR  
16 CLAIMS THERE, TO SUPPORT THEIR . . . THE DESCRIBED PROCESS.

17 Q. WHAT DO YOU MEAN BY "PILOT STUDY DATA"?

18 A. WELL, IT'S STANDARD WHEN SUBMITTING AN APPLICATION TO -- IF  
19 YOU HAVE ANY PRELIMINARY DATA WHICH SUPPORTS THE APPROACH THAT  
20 YOU'RE TAKING, YOU GIVE THAT -- PRESENT THAT TO THE REVIEW  
21 COMMITTEE SO THEY CAN FORM A JUDGMENT AS TO WHETHER THIS IS  
22 GOING TO WORK OR NOT. THAT'S LACKING HERE, SO I ASSUME THEY  
23 DON'T HAVE IT.

24 Q. NOW, THERE'S ONE OTHER PARAGRAPH IN THIS GRANT THAT I'D LIKE  
25 TO CALL TO YOUR ATTENTION. IT'S ON PAGE 5. AND WE'VE TAKEN IT

5

1 OUT HERE AND PUT IT ON THE POSTER B-244.

2 IT READS THAT THE DNA -- OH, IT'S ENTITLED,

3 "REPLICATION OF SYNTHETIC GENES."

4 AND IT SAYS: "DNA POLYMERASE -- POLYMERASES

5 CONTINUE TO BE THE SUBJECT OF STUDY WITH A VIEW TO THE

6 ACCURATE REPLICATION OF THE SYNTHETIC CHEMICALLY

7 DEFINED DEOXYPOLYNUCLEOTIDE CHAINS. ONCE SYNTHETIC

8 WORK HAS AFFORDED A PARTICULAR SEQUENCE, IT IS HOPED

9 THAT A DNA POLYMERASE CAN INSURE ITS PERMANENT

10 AVAILABILITY."

11 DOES -- IS THAT PARAGRAPH TALKING ABOUT THE SAME

12 PROJECT?

13 A. I BELIEVE IT IS, YES.

14 Q. DO YOU INTERPRET THAT PARAGRAPH TO SAY THAT DR. KHORANA HAD

15 ALREADY COMPLETED WORK WHICH GAVE HIM A METHOD FOR REPLICATING

16 THE SYNTHETIC GENES?

17 A. NO. IT'S SAYING QUITE SPECIFICALLY THAT IT'S HOPED THAT

18 THEY CAN DO THIS, BUT THERE'S NO INDICATION IN THAT PARAGRAPH

19 THAT THEY'VE DONE IT.

20 (PAUSE IN PROCEEDINGS)

21 Q. (BY MR. PASAHOW) NOW, IF IN MARCH OF 1984 AN

22 ORDINARILY-SKILLED POST-DOCTORAL FELLOW HAD FOUND OUT THAT DR.

23 MULLIS HAD BEEN SUCCESSFUL IN INVENTING THE PROCESS WHICH IS

24 DESCRIBED IN CLAIM 1 OF THE '202 PATENT BUT THAT POST-DOCTORAL

25 FELLOW HAD NO IDEA HOW DR. MULLIS HAD ACCOMPLISHED THE

5

1 EXPONENTIAL AMPLIFICATION, DO YOU THINK THAT PERSON WOULD BE  
2 ABLE TO DUPLICATE DR. MULLIS' INVENTION USING THE KLEPPE ARTICLE  
3 AS A GUIDE?

4 A. I DON'T SEE HOW HE COULD, BECAUSE THE CONDITIONS ARE . . .  
5 ARE NOT APPROPRIATE, AS DESCRIBED IN THAT PAPER.

6 Q. DO YOU THINK THE -- THAT THAT ORDINARILY-SKILLED  
7 POST-DOCTORAL FELLOW IN 1984 COULD HAVE DUPLICATED DR. MULLIS'  
8 INVENTION USING THE NATIONAL SCIENCE FOUNDATION PAPER WE'VE SEEN  
9 AS A GUIDE?

10 A. NO. THERE'S NO INFORMATION IN THERE REGARDING HOW THE  
11 REACTION WOULD BE DONE.

12 Q. AND IN GOING ON, DO YOU THINK HE COULD DUPLICATE DR. MULLIS'  
13 INVENTION USING THE PANET ARTICLE AS A GUIDE?

14 A. NO, FOR THE SAME REASONS. IT WOULDN'T BE HELPFUL.

15 Q. WOULD IT -- WOULD IT MATTER IF, INSTEAD OF LOOKING AT THESE  
16 PIECES INDIVIDUALLY, THE ORDINARILY-SKILLED POST-DOCTORAL FELLOW  
17 IN 1984 TOOK ALL THREE TOGETHER AS A GUIDE AND PUT THEM TOGETHER  
18 WITH WHATEVER KNOWLEDGE HE OR SHE HAD ABOUT THE RELEVANT  
19 PRINCIPLES?

20 A. I DON'T SEE HOW. NO ONE SINGLY IS HELPFUL, AND THE THREE  
21 TOGETHER DON'T REALLY PROVIDE THE ADDITIONAL INFORMATION.

22 Q. NOW, IN THIS HYPOTHETICAL, I SUGGESTED THAT SOMEHOW THE --  
23 THIS POST-DOCTORAL FELLOW FINDS OUT THAT DR. MULLIS HAS ALREADY  
24 SUCCESSFULLY MADE THIS REACTION WORK.

25 IN RESEARCH IN THE LABORATORY, DOES IT MATTER IF YOU

5 1 KNOW IN ADVANCE WHETHER OR NOT A PROCESS YOU'RE WORKING ON CAN  
2 SUCCESSFULLY BE DONE?

3 A. I THINK IT'S VERY, VERY IMPORTANT. IF -- IF YOU KNOW  
4 SOMETHING CAN BE DONE, YOU'RE GOING TO -- NORMALLY, YOU'RE GOING  
5 TO BE MUCH MORE PERSISTENT IN EXPLORING CONDITIONS TO TRY TO GET  
6 IT TO WORK.

7 THIS IS NOT UNUSUAL IN THE RESEARCH WORLD, TO HEAR A  
8 RUMOR ABOUT WHAT'S HAPPENED IN SOMEBODY'S LAB AND SUDDENLY YOU  
9 START DOING IT. AND . . . AND IF YOU WORK REAL HARD AT IT,  
10 TAKING SOME OF THE CLUES THAT YOU HEAR, YOU CAN SOMETIMES  
11 REPRODUCE THAT WORK.

6 12 BUT . . . IF YOU DON'T KNOW AHEAD OF TIME THAT  
13 SOMETHING IS GOING TO WORK, YOU OFTEN TEND TO BE DISCOURAGED BY  
14 THE FIRST FEW EXPERIMENTS THAT YOU DO.

15 Q. NOW, I'D LIKE TO LOOK AT A COUPLE OF OTHER ITEMS ON THIS  
16 TIMELINE FOR A MINUTE.

17 THERE WAS ALSO TESTIMONY THAT A MAJOR TEXTBOOK BY DR.  
18 KORNBERG, DNA SYNTHESIS, CAME OUT IN 1974, AND THEN THAT A -- A  
19 NEW VERSION OF THAT BOOK RE-TITLED DNA REPLICATION CAME OUT IN  
20 1980, AND THAT A SUPPLEMENT TO THAT 1980 BOOK CAME OUT IN 1982,  
21 AND THAT NONE OF THOSE HAD IN THEM ANY DISCUSSION OF THE PCR  
22 PROCESS.

23 WOULD THE ABSENCE OF ANY MENTION OF THE PCR PROCESS IN  
24 THESE SERIES OF TEXTBOOKS BY DR. KORNBERG HAVE ANY EFFECT ON THE  
25 1984 ORDINARILY-SKILLED POST-DOC'S ABILITY TO PERFORM THE

6  
1 INVENTION THAT DR. MULLIS MADE?

2 A. YES, INDEED. THOSE BOOKS CONTAIN VIRTUALLY EVERY REFERENCE  
3 TO THE REPLICATION PROCESS, AND THE ABSENCE OF ANY INFORMATION  
4 IN THOSE BOOKS WOULD -- WOULD BE . . . IT WOULD BE DISCOURAGING.  
5 IT WOULD NOT GIVE HIM ANY CLUES AS TO REFERENCES TO LOOK AT AND  
6 SO ON.

7 Q. THERE ARE -- THERE ARE TWO OTHER BOOKS ON HERE. ONE IS, IN  
8 1982, THERE WAS A PUBLICATION, THE MOLECULAR CLONING MANUAL --  
9 THE MOLECULAR CLONING LABORATORY MANUAL.

10 A. UH-HUH.

11 Q. ARE YOU FAMILIAR WITH THAT BOOK?

12 A. YES. WE'VE USED THAT -- WE USED THAT 1982 EDITION FOR  
13 SEVERAL YEARS IN THE LABORATORY.

14 Q. WE MARKED THAT BOOK AS EXHIBIT B-85, AND LET ME SHOW YOU A  
15 COPY.

16 IS THAT IT?

17 A. YES, THAT'S IT.

18 Q. WHO USES THAT BOOK?

19 A. WELL, THERE'S A MORE RECENT EDITION NOW, BUT THIS -- THIS  
20 BOOK WAS USED IN VIRTUALLY EVERY MOLECULAR BIOLOGICAL LABORATORY  
21 IN THE COUNTRY AS A SOURCE BOOK FOR METHODOLOGY -- METHODS,  
22 TECHNIQUES OF ALL SORTS THAT ARE USEFUL IN THE FIELD OF  
23 MOLECULAR BIOLOGY.

24 Q. THE BOOK IS PUBLISHED BY COLD SPRINGS -- COLD SPRING HARBOR  
25 LABORATORY.

6 1 WHAT IS THAT?

2 A. COLD SPRING HARBOR LABORATORY IS A WORLD FAMOUS LABORATORY  
3 WITH OUTSTANDING SCIENTISTS ON ITS STAFF, AND ALSO IT'S -- IT'S  
4 BEEN A CENTER FOR THE TEACHING OF MOLECULAR BIOLOGY AND  
5 BIOLOGICAL SYSTEMS TO SCIENTISTS OVER A SPAN OF MANY YEARS.

6 SCIENTISTS WHO WANT TO MOVE IN A PARTICULAR AREA FOR  
7 INVESTIGATION OFTEN ENTER INTO COURSES IN THE SUMMER THERE WHICH  
8 ARE VERY INTENSIVELY TAUGHT, AND YOU ESSENTIALLY WORK 16 HOURS A  
9 DAY DOING EXPERIMENTS BASICALLY TO LEARN TECHNIQUES IN A NEW  
10 AREA OF SCIENCE THAT YOU WANT TO GO INTO.

11 SO THE COLD SPRING HARBOR REALLY IS AN EDUCATIONAL  
12 INSTITUTION, IN A SENSE.

13 Q. WOULD THE ABSENCE OF ANY MENTION OF THE PCR PROCESS IN THE  
14 1982 MANUAL AFFECT THE ABILITY OF A POST-DOCTORAL FELLOW IN 1984  
15 TO BE ABLE TO DO THAT PROCESS?

16 A. ABSOLUTELY. IT WOULD . . . IT WOULD TELL THAT PERSON THAT  
17 SUCH A MECHANISM DIDN'T WORK -- DIDN'T EXIST, ESSENTIALLY.

18 Q. NOW, YOU MENTIONED THAT THERE'S A NEW EDITION OF THAT BOOK,  
19 AND WE'VE ALSO MARKED THAT AS EVIDENCE -- IN EVIDENCE AS EXHIBIT  
20 B-85. LET ME SHOW YOU THAT.

21 AND OBVIOUSLY IT'S GOTTEN MUCH LARGER.

22 A. YES.

23 Q. ARE YOU FAMILIAR WITH THE NEW EDITION OF THE BOOK?

24 A. YES. WE HAVE THESE COPIES IN MY LABORATORY.

25 Q. AND THIS CAME OUT IN 1989; IS THAT CORRECT?

6

1 A. YES.

2 Q. AND DOES THE 1989 BOOK HAVE ANY INFORMATION ABOUT THE PCR  
3 PROCESS?

4 A. YES, IT DOES.

5 Q. IS IT THE SUBJECT OF ITS OWN CHAPTER IN THAT BOOK?

6 A. I WOULD HAVE TO LOOK. PROBABLY IT IS. I -- I HAVEN'T  
7 LOOKED AT IT RECENTLY.

8 Q. COULD YOU CONFIRM THAT FOR US, PLEASE.

9 A. LET'S SEE IF I CAN FIND THE INDEX HERE.

10 (PAUSE IN PROCEEDINGS)

11 THE WITNESS: IT'S CHAPTER 14. I GUESS IT'S IN VOLUME  
12 2 HERE.

13 (PAUSE IN PROCEEDINGS)

14 THE WITNESS: YES. IT'S A WHOLE CHAPTER, "IN VITRO  
15 AMPLIFICATION OF DNA BY THE POLYMERASE CHAIN REACTION." AN  
16 ENTIRE CHAPTER.

17 Q. (BY MR. PASAHOW) WHY HAS THE ONE-VOLUME BOOK BECOME THREE  
18 VOLUMES? IS THAT EXPLAINED SOMEWHERE?

19 A. WELL, THIS -- THIS INDICATES THE PACE OF RESEARCH IN THE  
20 COUNTRY. THERE ARE THAT MANY MORE TECHNIQUES AND VARIATIONS ON  
21 TECHNIQUES THAT HAVE TO BE DESCRIBED. OF COURSE, THE POLYMERASE  
22 CHAIN REACTION IS ONE OF THOSE.

23 Q. IN THE BEGINNING OF THE FIRST VOLUME, IN THE PREFACE, THE  
24 AUTHORS HAVE THIS DISCUSSION OF THE INCREASE IN SIZE, WHICH THEY  
25 SAY:

6 1 "THIS INCREASE" --

2 THEY TALK ABOUT THE DEVELOPMENTS. THEY SAY:

3 "THIS INCREASE IN THE RANGE AND SPEED OF  
4 MOLECULAR CLONING IS REFLECTED IN THE TRIPLING OF SIZE  
5 OF THIS MANUAL AND ITS CONSEQUENT DIVISION INTO THREE  
6 VOLUMES. TECHNIQUES THAT WERE MENTIONED ONLY IN  
7 PASSING IN THE FIRST EDITION, SUCH AS MUTAGENESIS,  
8 EXPRESION OF CLONED GENES IN MAMMALIAN CELLS, AND  
9 DIDEOXY-MEDIATED SEQUENCING, ARE NOW DESCRIBED IN  
10 DEPTH; NEW SECTIONS HAVE BEEN ADDED THAT DEAL WITH  
11 RECENTLY INVENTED TECHNIQUES, SUCH AS AMPLIFICATION OF  
12 DNA BY THE POLYMERASE CHAIN REACTION; AND WE HAVE  
13 INCLUDED MODERN VARIATIONS AND EMBELLISHMENTS OF MANY  
14 OF THE BASIC METHODS THAT WERE THE MAINSTAY OF THE  
15 FIRST EDITION."

16 NOW, ARE YOU FAMILIAR WITH THE EDITORS OF THIS BOOK?

17 A. YES. I KNOW TWO OF THEM: SAMBROOK AND MANIATIS.

18 Q. ARE THEY IN A POSITION TO BE FAMILIAR WITH THE CURRENT  
19 DEVELOPMENTS IN MOLECULAR BIOLOGY?

20 A. OH, YES, ABSOLUTELY. THEY'RE LEADERS IN THEIR RESPECTIVE  
21 AREAS.

22 Q. NOW, ONE OTHER ITEM ON THIS TIMELINE:

23 IN DECEMBER 1985, THE SAIKI, ET AL., ARTICLE CAME OUT  
24 IN THE SCIENCE MAGAZINE. AND I BELIEVE YOU INDICATED YOU WERE  
25 FAMILIAR WITH THAT?

7

1 A. YES.

2 Q. I'LL SHOW YOU A COPY. IT'S EXHIBIT B-38.

3 AND IT'S CORRECT THAT DR. MULLIS IS AMONG THE SEVERAL  
4 AUTHORS OF THAT ARTICLE; IS THAT RIGHT?

5 A. THAT'S RIGHT.

6 Q. DO YOU KNOW WHO DR. SAIKI IS?

7 A. YES. SHE'S ONE OF THE YOUNGER SCIENTISTS AT CETUS WHO  
8 WORKED WITH DR. MULLIS AND DR. ERLICH ON THIS MANUSCRIPT.

9 Q. NOW, BEFORE THAT ARTICLE CAME OUT IN DECEMBER 1985, HAD YOU  
10 EVER HEARD OF ANYONE DOING THE PCR PROCESS OUTSIDE OF CETUS  
11 CORPORATION?

12 A. NO.

13 Q. WOULD IT HAVE BEEN USEFUL BEFORE DECEMBER 1985?

14 A. IT CERTAINLY WOULD HAVE BEEN.

15 Q. WHAT WOULD IT HAVE BEEN USEFUL FOR?

16 A. WELL, ESSENTIALLY FOR THE SAME THINGS THAT WE USE IT FOR  
17 TODAY.

18 THERE WAS A WHOLE PERIOD FROM, I'D SAY, ABOUT 1976 OR  
19 '77 UP TO 1985 WHERE PCR COULD HAVE BEEN PERFORMED IN A  
20 PRACTICAL WAY BUT WE DIDN'T HAVE THE TECHNIQUE. THERE WERE MANY  
21 THINGS THAT COULD HAVE BEEN DONE WITH IT.

22 (PAUSE IN PROCEEDINGS)

23 Q. (BY MR. PASAHOW) NOW, DR. KORNBERG WAS DISCUSSING WITH US  
24 THE SUPPLEMENT TO HIS BOOK, AND HE TOLD US THAT WHEN THE PUB --  
25 WHEN THE SUPPLEMENT WAS PUBLISHED IN 1982, "PCR WOULD HAVE BEEN

7

1 A PRACTICAL PROCESS IF IT HAD BEEN DEVELOPED AT THAT TIME."

2 DO YOU BELIEVE THAT'S RIGHT?

3 A. IN 1982?

4 Q. YES, SIR.

5 A. OH, YES, YES. THAT'S CORRECT.

6 Q. IS IT SOMETHING YOU WOULD HAVE USED --

7 A. YEAH.

8 Q. -- IN THE LABORATORIES AT JOHNS HOPKINS IF IT HAD BEEN  
9 AVAILABLE?

10 A. IN 19 -- IN 1982, YES. YES, IT WOULD HAVE BEEN VERY USEFUL.

11 Q. AS OF THAT TIME, WERE PRIMERS AVAILABLE TO -- TO PEOPLE SUCH  
12 AS YOURSELF?

13 A. PRIMERS WERE BECOMING VERY READILY AVAILABLE BY 1982.

14 Q. WERE THE NECESSARY DNA POLYMERASES AVAILABLE AT THAT TIME?

15 A. THEY WERE ALL COMMERCIALY AVAILABLE.

16 Q. DID YOU HAVE SEQUENCE INFORMATION NECESSARY TO MAKE THE  
17 PRIMERS AT THAT TIME?

18 A. BY 1982 . . . I DON'T KNOW HOW MANY MILLIONS OF BASE PAIRS  
19 WERE SEQUENCED AT THAT POINT, BUT THERE WAS A GREAT DEAL OF  
20 INFORMATION. AND IN MY OWN LABORATORY, WE'D SEQUENCED SEVERAL  
21 GENES AT THAT POINT.

22 Q. NOW, THERE'S BEEN A DISCUSSION OF A PROCESS CALLED GEL  
23 ELECTROPHORESIS.

24 ARE YOU FAMILIAR WITH THAT?

25 A. YES, VERY MUCH SO. IT'S ONE OF OUR MOST USEFUL TECHNIQUES.

7  
1 Q. WHAT IS IT USED FOR?

2 A. WELL, GEL ELECTROPHORESIS IS A VERY POWERFUL METHOD FOR  
3 SEPARATING DISCRETE PIECES OF DNA FROM EACH OTHER.

4 FOR EXAMPLE, IF YOU CUT A VIRAL GENOME WITH A  
5 RESTRICTION ENZYME INTO, LET'S SAY, A HALF A DOZEN PIECES OF  
6 DIFFERENT LENGTHS, YOU CAN LOAD THEM INTO A SLOT ON THIS -- IT'S  
7 A GEL USUALLY BETWEEN TWO GLASS PLATES.

8 AND YOU LOAD THE DNA SAMPLES IN A LITTLE SLOT AT THE  
9 TOP, AND THEN YOU APPLY AN ELECTRIC CURRENT ACROSS -- DOWN  
10 THROUGH THE GEL.

11 THE DNA MOLECULES WHICH ARE CHARGED MOVE IN THE  
12 ELECTRICAL FIELD DOWN TOWARDS THE BOTTOM OF THE PLATE. THE  
13 BIGGER FRAGMENTS MOVE MORE SLOWLY THAN THE SMALL ONES. THE  
14 SMALL ONES CAN GO THROUGH THE GEL MORE READILY.

15 IT'S A VERY USEFUL TECHNIQUE.

16 Q. WHEN DID YOU START USING GEL ELECTROPHORESIS IN YOUR  
17 LABORATORIES?

18 A. WELL, IN MY OWN LABORATORY, WE WERE USING IT EXTENSIVELY  
19 BY . . . I WOULD SAY, AROUND 1973.

20 Q. WAS IT USED AT JOHNS HOPKINS BEFORE THAT?

21 A. YES, IT WAS. IN THE LABORATORY DOWN THE HALL, MY COLLEAGUE  
22 DR. NATHANS, WHO SHARED THE NOBEL PRIZE WITH ME, HAD DONE HIS  
23 WORK REGARDING THE NOBEL PRIZE AWARD IN THE PERIOD FROM ABOUT  
24 1969 TO 1971, AND HE PUBLISHED A PAPER, I BELIEVE, IN 1971  
25 DESCRIBING THAT WORK, AND IT WAS BASED ON USING GEL

7  
1 ELECTROPHORESIS TO SEPARATE RESTRICTION FRAGMENTS OF A SMALL  
2 VIRUS. IT WAS ONE OF THE FIRST DEMONSTRATIONS OF THE UTILITY OF  
3 RESTRICTION ENZYMES.

4 Q. NOW, IF PCR HAD BEEN DEVELOPED IN ~~1969~~ OR ~~1970~~, IS THAT  
5 SOMETHING THAT YOU WOULD HAVE BEEN INTERESTED IN KNOWING?

6 A. I THINK FROM A THEORETICAL STANDPOINT, IT WOULD HAVE BEEN  
7 VERY INTERESTING. I DON'T THINK IT WOULD HAVE RECEIVED WIDE  
8 PRACTICALITY AT THAT POINT.

9 Q. WERE THERE -- WERE THERE OTHERS BESIDES YOURSELF WHO WOULD  
10 HAVE BEEN INTERESTED IN KNOWING OF THAT DEVELOPMENT IN THE  
11 1969-1970 PERIOD?

12 A. I THINK MOST SCIENTISTS WOULD HAVE BEEN INTERESTED IN THAT  
13 APPLICATION OF THE DNA POLYMERASE.

14 Q. DID THE SCIENTISTS WHO'D BE INTERESTED IN A TECHNIQUE LIKE  
15 THAT HAVE PUBLICATIONS THAT THEY REGULARLY READ?

16 A. YES, CERTAINLY.

17 Q. WHAT WERE THOSE PUBLICATIONS?

18 A. YEAH. THERE WERE . . . WELL, EVERYBODY HAS THEIR OWN  
19 FAVORITE PUBLICATIONS, OF COURSE, BUT I THINK THE KEY ONES AT  
20 THAT TIME WERE JOURNALS LIKE SCIENCE, NATURE, JOURNAL OF  
21 BIOLOGICAL CHEMISTRY, JOURNAL OF MOLECULAR BIOLOGY, NUCLEIC  
22 ACIDS RESEARCH, JUST TO NAME A FEW. THERE ARE USUALLY ABOUT  
23 MAYBE A HALF A DOZEN, UP TO 10, JOURNALS THAT WERE WIDELY READ.

24 Q. NOW, ONE LAST AREA:

25 DR. KORNBERG DESCRIBED FOR US SOMETHING OF THE PROCESS

8 1 ONE WOULD GO THROUGH IN ORDER TO MAKE A PCR REACTION OR A  
2 PROCESS LIKE THAT WORK WHERE THERE ARE A LOT OF DIFFERENT  
3 CONDITIONS, ALL OF WHICH HAVE TO BE COORDINATED, AND YOU HAVE TO  
4 CHOOSE THE RIGHT ONES FOR EACH OF THOSE CONDITIONS.

5 A. UH-HUH.

6 Q. AND HE EXPLAINED THAT, IN THE LABORATORY, IT'S SOMETHING OF  
7 AN ART FORM, THAT ALL OF THE POSSIBILITIES WOULD TAKE FOREVER,  
8 AND SO A SCIENTIST GOES THROUGH THEM USING INSIGHTS, INTUITION,  
9 HIS PRE-EXISTING KNOWLEDGE, TRYING TO FIND THE ONES THAT WORK.

10 HAVE YOU OBSERVED THAT PHENOMENON?

11 A. YES. I WOULD AGREE COMPLETELY WITH WHAT DR. KORNBERG SAID.

12 IT'S NOT A STRAIGHTFORWARD EXERCISE FOR EVEN A SKILLED  
13 POST-DOCTORAL FELLOW TO NECESSARILY -- TO WORK OUT A PROCEDURE,  
14 PARTICULARLY ONE THAT INVOLVES MANY COMBINATIONS OF POSSIBLE  
15 REACTION CONDITIONS. YOU HAVE TO UTILIZE YOUR INTUITION,  
16 INVENTIVENESS, KNOWLEDGE, THEORETICAL KNOWLEDGE THAT YOU'VE  
17 ACQUIRED BY EXPERIENCE.

18 Q. WHY DOES IT TAKE SO LONG TO DO SOMETHING LIKE THAT?

19 A. WELL, I THINK I COULD . . . WELL, LET'S JUST TAKE THE CASE  
20 OF THE PCR REACTION ITSELF.

21 WHAT ARE THE VARIOUS PARAMETERS THAT ONE WOULD HAVE TO  
22 INVESTIGATE TO TRY TO GET THAT REACTION TO GO IF YOU DIDN'T KNOW  
23 HOW TO DO IT?

24 YOU -- YOU COULD VARY THE PRIMER CONCENTRATION, FOR  
25 EXAMPLE, MAYBE CHOOSE 10 DIFFERENT RANGES OF PRIMER

8  
1 CONCENTRATION; YOU ALSO WOULD HAVE TO VARY THE TEMPLATE OVER A  
2 RANGE, PERHAPS ANOTHER 10 POSSIBLE CONCENTRATIONS.

3 (PAUSE IN PROCEEDINGS)

4 THE WITNESS: THE -- THE PRIMER AND TEMPLATE ARE GOING  
5 TO BE ANNEALED TOGETHER; THEY HAVE TO BE -- THE TEMPLATE HAS TO  
6 BE DENATURED. OF COURSE, THAT -- YOU COULD USE DIFFERENT TIMES  
7 FOR THAT. THE ANNEALING, YOU MIGHT CHOOSE VERY SHORT TIMES OR  
8 LONG TIMES FOR THE ANNEALING.

9 THE BUFFER CONDITIONS, MAGNESIUM CONCENTRATION, THE  
10 AMOUNT OF THE DNA POLYMERASE, ALL OF THOSE THINGS WOULD HAVE TO  
11 BE VARIED. AND YOU ATTEMPT TO BALANCE THEM OUT SO AS TO GET  
12 THIS REACTION TO GO THROUGH MULTIPLE CYCLES.

13 IF YOU THINK ABOUT THE POSSIBLE NUMBER OF COMBINATIONS,  
14 IT'S 10 TIMES 10 TIMES 10 TIMES 10, BUT IT COULD BE UP TO A  
15 MILLION OR MORE COMBINATIONS IF YOU WENT THROUGH A REASONABLE  
16 RANGE OF -- OF EACH OF THE PARAMETERS.

17 SO, I MEAN, THAT'S LITERALLY IMPOSSIBLE TO DO  
18 EXHAUSTIVELY. ONE HAS TO USE A LITTLE BIT OF THE CREATIVENESS,  
19 THE INVENTIVENESS, TO TRY TO NARROW THAT DOWN. AND I THINK  
20 THAT'S EXACTLY WHAT DR. KORNBERG WAS SAYING.

21 MR. PASAHOW: THANK YOU.

22 I HAVE NOTHING FURTHER, YOUR HONOR.

23 THE COURT: THANK YOU.

24 (PAUSE IN PROCEEDINGS)

25 MR. FIGG: YOUR HONOR, WE HAVE SOME -- AN OVERHEAD

8 1 PROJECTOR TO SET UP. I DON'T KNOW IF THIS IS A LITTLE EARLY FOR  
2 OUR BREAK, BUT -- HOW WOULD YOU --

3 THE COURT: IT IS.

4 HOW LONG DO YOU EXPECT TO BE ON CROSS?

5 MR. FIGG: ON CROSS IN TOTAL?

6 THE COURT: YES.

7 MR. FIGG: OH, HOURS, IT PROBABLY LOOKS LIKE.

8 THE COURT: UH-HUH. WELL, FINE. WHY DON'T WE DO THAT  
9 NOW, THEN, AND HAVE -- HOW LONG WILL IT TAKE TO SET IT UP?

10 MR. FIGG: OH, JUST A FEW MINUTES.

11 THE COURT: WHY DON'T WE TAKE 10 MINUTES NOW.

12 THIS IS YOUR FIRST BREAK. YOU WON'T GET ONE FOR  
13 AWHILE. AND THEN WE'LL HAVE THAT SET UP.

14 ARE YOU GOING TO NEED THESE ITEMS HERE?

15 MR. FIGG: NOT THIS. WE JUST NEED ONE EASEL.

16 THE COURT: JUST ONE EASEL? OKAY.

17 YOU MAY STEP DOWN, IF YOU WISH TO DO SO. THANK YOU.

18 YOU MAY GO BACK TO THE JURYROOM. YOU'RE GOING TO HAVE  
19 TO HANDLE THE DOOR YOURSELVES TODAY.

20 (JURY EXCUSED)

21 (OPEN COURT, JURY NOT PRESENT:)

22 THE COURT: YOU, I ASSUME, RECEIVED A COPY OF  
23 DEFENDANT'S MOTION. ARE WE STILL ON THE THURSDAY DATE FOR THAT?

24 MR. FIGG: WELL, WE RECEIVED IT. WE LOOKED AT IT LAST  
25 NIGHT. I THINK A LITTLE MORE TIME WOULD BE HELPFUL TO US.

8 1 THE COURT: CAN YOU GET IT IN BY THE END OF FRIDAY?

2 MR. FIGG: THAT WOULD HELP.

3 THE COURT: BECAUSE WE'RE GOING TO HAVE TO RULE ON IT,  
4 TOO, AT SOME POINT --

5 MR. FIGG: I UNDERSTAND, YES.

6 THE COURT: -- WHICH MEANS READING THE PAPERS. AND I'D  
7 LIKE TO RULE ON IT ON MONDAY --

8 MR. FIGG: OKAY.

9 THE COURT: -- TAKE IT UP ON MONDAY AT SOME POINT.

10 MR. FIGG: WE'LL TRY TO GET IT IN BY FRIDAY.

11 THE COURT: OKAY. OKAY. AS A MATTER OF FACT, IF YOU  
12 CAN GET IT IN BY FRIDAY, SAY, NOONTIME OR 1:00 O'CLOCK, THAT  
13 WOULD HELP, SO WE HAVE AT LEAST FRIDAY AFTERNOON. OKAY.

14 MR. FIGG: OKAY.

15 THE COURT: THANK YOU.

16 (RECESS TAKEN AT 9:07 A.M.)

17

18

19

20

21

22

23

24

25

(CONTINUED ON NEXT PAGE, NOTHING OMITTED)

1 (OPEN COURT, JURY PRESENT:)

2 MR. FIGG: THANK YOU, YOUR HONOR.

3 CROSS-EXAMINATION

4 BY MR. FIGG:

5 Q. GOOD MORNING, DR. SMITH.

6 A. GOOD MORNING.

7 Q. DR. SMITH, I'D LIKE TO GO INTO YOUR RELATIONSHIP WITH CETUS  
8 FOR A BIT.

9 A. UH-HUH.

10 Q. YOU'VE BEEN A CONSULTANT TO CETUS SINCE 1980; IS THAT  
11 CORRECT?

12 A. 1980.

13 Q. GOING ON 11 YEARS NOW YOU'VE BEEN WORKING WITH CETUS?

14 A. THAT'S RIGHT.

15 Q. YOU'VE BEEN A MEMBER OF CETUS' SCIENTIFIC ADVISORY BOARD  
16 SINCE 1980?

17 A. YES.

18 Q. AND, AS I UNDERSTAND, THAT'S A BOARD COMPOSED OF SCIENTISTS  
19 WHO REVIEW WORK THAT'S GOING ON AT CETUS AND GIVES ADVICE TO  
20 CETUS ON WHAT THEY MIGHT DO TO IMPROVE THEIR SITUATION?

21 A. THAT'S RIGHT, YES.

22 Q. AND AS A RESULT OF THAT YOU'VE INTERACTED WITH A NUMBER OF  
23 CETUS SCIENTISTS OVER THE YEARS I WOULD IMAGINE?

24 A. YES, A NUMBER. ALTHOUGH, MY MAJOR INTERACTIONS WERE  
25 RELATIVELY SMALL NUMBER.

1 Q. I UNDERSTAND YOU ATTEND ALL OF THE ANNUAL CETUS SCIENTIFIC  
2 MEETINGS?

3 A. I THINK I MISSED THE ONE THIS YEAR. THEY MAY HAVE HAD SOME  
4 SMALL -- SMALLER GROUPS MEETING ANNUALLY THAT I MISSED, BUT THE  
5 BIG GENERAL MEETINGS I TRY TO ATTEND VERY REGULARLY.

6 Q. AND CETUS GIVES YOU COPIES OF SOME OF THEIR SCIENTIFIC  
7 PAPERS AND ASKS TO YOU REVIEW THEM AND COMMENT ON THEM BEFORE  
8 THEY SEND THEM OUT TO THE PUBLISHERS?

9 A. VERY FEW, YES.

10 Q. I UNDERSTAND YOU'RE AVAILABLE BY TELEPHONE TO CETUS  
11 SCIENTISTS SO THEY CAN CALL YOU AND CONSULT WITH YOU FROM TIME  
12 TO TIME?

13 A. GENERALLY IN REGARD TO GETTING SOMETHING PUBLISHED OR A  
14 QUESTION CONCERNING PARTICULAR METHODS OR WHATEVER I MIGHT HAVE  
15 EXPERTISE ON.

16 Q. I UNDERSTAND THAT AS A RESULT OF YOUR SERVING ON THE  
17 SCIENTIFIC ADVISORY BOARD CETUS . . . TENDERED OR GAVE TO YOU  
18 3,000 SHARES OF STOCK IN CETUS CORPORATION?

19 A. THAT'S CORRECT.

20 Q. YOU STILL OWN THAT STOCK TODAY?

21 A. NO, I DON'T.

22 Q. YOU'RE RECEIVING A CONSULTING FEE, AN ANNUAL CONSULTING FEE  
23 FOR YOUR CONSULTATIONS WITH CETUS?

24 A. THAT'S RIGHT.

25 Q. IN ADDITION YOU'RE BEING COMPENSATED FOR THIS EFFORT IN THIS

1 LAWSUIT?

2 A. FOR THE TESTIMONY AND PREPARATION, YES.

3 Q. DR. SMITH, YOU INDICATED THAT YOU'VE DONE CONSIDERABLE WORK  
4 IN THE AREA OF RESTRICTION ENZYMES, I BELIEVE?

5 A. YES.

6 Q. AND RESTRICTION ENZYMES ARE ENZYMES THAT CUT DNA INTO  
7 PIECES?

8 A. THAT'S CORRECT.

9 Q. THAT'S ACTUALLY BEEN THE MAJOR FOCUS OF YOUR SCIENTIFIC WORK  
10 OVER THE LAST COUPLE OF DECADES; IS THAT RIGHT?

11 A. WELL, IT'S BEEN ONE OF THE MAJOR AREAS. I DO ALSO -- I  
12 WOULD SAY IT'S LESS SO NOW THAN IT WAS IN THE 1970'S, 1980  
13 PERIOD, BUT I'M STILL CONTINUING THAT.

14 Q. NOW, RESTRICTION ENZYMES ARE COMPLETELY DIFFERENT IN THEIR  
15 FUNCTION THAN DNA POLYMERASE; IS THAT CORRECT?

16 A. THAT IS CORRECT.

17 Q. DNA POLYMERASE MAKES DNA, AND RESTRICTION ENZYMES CLIP IT AT  
18 SPECIFIC POINTS?

19 A. THAT'S CORRECT.

20 Q. AND RESTRICTION ENZYMES, ALTHOUGH I UNDERSTAND THEY MAY BE  
21 USED IN CLONING AND PREPARING DNA, BUT AM I CORRECT THAT  
22 RESTRICTION ENZYMES ARE NOT USED IN THE PCR PROCESS AT ALL, IN  
23 THE PROCESS ITSELF?

24 A. IN THE PROCESS ITSELF, NO.

25 Q. AM I ALSO CORRECT THAT YOU HAVE -- YOU'VE NEVER PUBLISHED

1 ANY SCIENTIFIC WORK WHERE YOU WERE STUDYING THE ACTIVITIES OR  
2 PROPERTIES OF DNA POLYMERASE?

3 A. THAT IS CORRECT.

4 Q. YOU'VE USED IT FROM TIME TO TIME?

5 A. I'VE USED IT FOR A NUMBER OF PRIMARILY LABELING METHODS,  
6 THINGS OF THAT SORT, BUT NEVER INVESTIGATING THE PROPERTIES OF  
7 THOSE ENZYMES, THAT'S RIGHT.

8 Q. YOU'VE USED IT BASED ON THE TEACHINGS OF OTHERS?

9 A. THAT'S CORRECT.

10 Q. YOU FOLLOWED TEACHINGS OF PEOPLE LIKE DR. KORNBERG, I  
11 SUPPOSE?

12 A. THAT IS CORRECT.

13 Q. YOU INDICATED THAT YOU'VE USED IT IN LABELING. WHAT DO YOU  
14 MEAN BY THAT?

15 A. WELL, WE'VE USED IT EXTENSIVELY TO DO WHAT'S CALLED NICK  
16 TRANSLATION, IN WHICH YOU -- IF YOU WANT TO LABEL A PARTICULAR  
17 MOLECULE YOU INTRODUCE A FEW NICKS WITH A RANDOM NUCLEASE AND  
18 THEN THE POLYMERASE CAN TRANSLATE THOSE NICKS BY ADDING  
19 RADIOACTIVE NUCLEOTIDES.

20 MEANWHILE WITH THE FIVE-PRIME RADIOACTIVITY YOU'RE  
21 MOVING THE STRANDS, THE NICK LITERALLY MOVES ALONG. VERY USEFUL  
22 WAY TO LABEL DNA.

23 Q. YOU'RE REPLACING ONE OF THE STRANDS WITH AN IDENTICAL STRAND  
24 WHICH HAS RADIOACTIVE NUCLEOTIDES WITHIN IT?

25 A. THAT'S RIGHT.

2

1 Q. WHAT DO YOU USE THAT FOR?

2 A. WELL, WE'VE -- IN AN EXPERIMENT THAT I CAN THINK OF MOST  
3 OBVIOUSLY WE USED IT TO LABEL DONOR DNA THAT WE WERE GOING TO  
4 INTRODUCE INTO CELLS IN GENTIC TRANSFORMATION.

5 Q. HAVE YOU USED THAT TECHNIQUE TO MAKE HYBRIDIZATION PROBES?

6 A. POST-DOCTORAL FELLOWS IN THE LABORATORY HAVE, YES.

7 Q. POST-DOCS WORKING UNDER YOUR SUPERVISION?

8 A. YEAH.

9 Q. WAS THAT KIND OF WORK GOING ON BEFORE 1984?

10 A. I DON'T THINK SO. NOT IN MY LABORATORY. I COULD BE WRONG  
11 BY A YEAR OR TWO THERE.

12 Q. LET ME ASK IT THIS WAY:

13 THAT TECHNIQUE WAS GENERALLY KNOWN AND USED BY  
14 SCIENTISTS IN THE FIELD BEFORE 1984, WASN'T IT?

15 A. THE NICK TRANSLATION?

16 Q. THE NICK TRANSLATION.

17 A. OH, YEAH.

18 Q. USING THE PRODUCT OF THAT NICK TRANSLATION AS A PROBE FOR  
19 DETECTION?

20 A. I THINK SO, YES.

21 Q. MR. PASAHOW SHOWED YOU A COPY OF CLAIM 1 OF THE '195. AM I  
22 CORRECT THAT THAT PROCESS WE'VE JUST BEEN TALKING ABOUT, MAKING  
23 A PROBE AND USING IT FOR HYBRIDIZATION, IS THE PROCESS THAT IS  
24 REFERRED TO IN STEPS D AND E OF CLAIM 1 OF THE '195?

25 A. NOT EXACTLY, BECAUSE THE LABEL PROBE THERE -- WELL, IT COULD

2

1 BE, YES, I'M SORRY, YOU COULD LABEL IT THAT WAY. THERE ARE  
2 OTHER WAYS OF LABELING.

3 Q. RIGHT. MANY WAYS OF MAKING A LABEL PROBE?

4 A. THAT'S CORRECT.

5 Q. SCIENTISTS WERE USING LABELED PROBES TO DETECT DNA --

6 A. SURE.

7 Q. -- ON A REGULAR BASIS BEFORE 1984?

8 A. YES.

9 Q. NOW, PRIMER EXTENSION IS A KEY ELEMENT OF PCR, RIGHT?

10 A. THAT IS CORRECT.

11 Q. AS I UNDERSTAND, YOU'VE NEVER DONE ANY WORK OR PUBLISHED ANY  
12 WORK IN WHICH YOU STUDIED THE MECHANISMS OF THE PRIMER EXTENSION  
13 REACTION?

14 A. NO, I'VE NEVER INVESTIGATED THAT.

15 Q. YOU'VE RELIED ON WORK OF OTHER PEOPLE?

16 A. THAT'S CORRECT.

17 Q. AND USED PRIMER EXTENSION IN YOUR RESEARCH?

18 A. PRIMARILY IN SEQUENCING, YES.

19 Q. AND SOME OF THE PEOPLE'S WORK THAT YOU'VE RELIED ON INCLUDE  
20 DR. KORNBERG?

21 A. THAT'S CORRECT.

22 Q. WOULD I BE CORRECT IN SAYING THAT YOU WOULD NOT CONSIDER  
23 YOURSELF TO HAVE GREATER EXPERTISE IN THE FIELD OF DNA  
24 POLYMERASE AND PRIMER EXTENSION THAN DR. KORNBERG HAS?

25 A. NO. CONSIDERABLY LESS.

2 1 Q. CONSIDERABLY LESS THAN DR. KORNBERG HAS?

2 A. IN TERMS OF THE VAST LITERATURE OF THE VARIOUS POLYMERASE,  
3 YES. CLEARLY THE AUTHORITY THERE.

4 Q. YOU SPENT A BIT OF TIME TALKING WITH MR. PASAHOW ABOUT SOME  
5 PAPERS THAT HAVE BEEN PUBLISHED BY DR. KHORANA'S LABORATORY, DO  
6 YOU RECALL THAT?

7 A. YES.

8 Q. THE KLEPPE PAPER AND SO FORTH?

9 A. YEAH.

10 Q. NOW, DR. KHORANA WAS WORKING IN AN ENTIRELY DIFFERENT FIELD  
11 THAN YOU WERE WORKING IN IN THE EARLY 1970'S, ISN'T THAT  
12 CORRECT?

13 A. THAT'S CORRECT.

14 Q. YOU WEREN'T FOLLOWING DR. KHORANA'S WORK?

15 A. I KNEW VERY WELL WHAT HE WAS DOING, BUT I DIDN'T -- DIDN'T  
16 READ HIS PAPERS.

17 Q. IN FACT --

18 A. I WOULD PERHAPS READ THE ABSTRACTS, BUT I DIDN'T SPEND MUCH  
19 TIME READING THE PAPERS.

20 Q. DID YOU FIND HIS WORK TO BE SOMEWHAT BORING TO YOU?

21 A. THEIR WORK ON THE -- NOT THE WORK IN THE '60'S TO WORKOUT  
22 THE GENTIC CODE THAT WAS EXTREMELY EXCITING, VERY BASIC WORK.

23 BUT THE APPLICATION OF HIS BEAUTIFUL ORGANIC SYNTHESIS  
24 METHODS FOR DNA, THE EMPLOYMENT OF HUNDREDS OF SCIENTISTS TO  
25 SYNTHESIZE THIS GENE, I KNEW WHAT HE WAS TRYING TO DO AND SIMPLY

2  
3  
1 WAITING FOR HIM TO FINISH IT. I DID FIND IT SOMEWHAT BORING.

2 Q. I UNDERSTAND YOU MENTIONED A NUMBER OF JOURNALS TO MR.  
3 PASAHOW WHERE SCIENTISTS PUBLISH THEIR WORK AND OTHER SCIENTISTS  
4 WOULD READ THOSE JOURNALS TO APPRIZE THEMSELVES OF WHAT WAS  
5 GOING ON. I THINK ONE OF THEM YOU MENTIONED WAS THE JOURNAL OF  
6 MOLECULAR BIOLOGY.

7 AM I CORRECT THAT BACK IN THE EARLY '70S, THERE WAS AN  
8 ENTIRE ISSUE OR AN ENTIRE VOLUME OF THE JOURNAL OF MOLECULAR  
9 BIOLOGY?

10 A. I REMEMBER IT WELL.

11 Q. THAT CONTAINED --

12 A. I THINK IT WAS 1972.

13 Q. WHAT CHARACTERIZED THAT 1972 VOLUME?

14 A. I -- I DON'T THINK I'VE EVER READ ONE OF THE PAPERS.

15 Q. WHAT WAS IN THAT 1972 VOLUME?

16 A. BUT THAT -- I BELIEVE WAS THE VOLUME WHERE HE DESCRIBED  
17 THE . . . THE WAY HE WENT ABOUT SYNTHESIZING THE FIRST TRNA  
18 GENE. I KNOW GENERALLY THE WAY IT WAS DONE.

19 I ALWAYS KEEP MYSELF UP WITH THE BASIC WAYS THAT THINGS  
20 THAT SCIENTISTS ARE DOING, BUT I DON'T NECESSARILY READ ALL THE  
21 PAPERS.

22 Q. THE POINT I WAS TRYING TO MAKE, IN FACT, EVERY PAPER IN THAT  
23 72 VOLUME WAS DR. KHORANA'S -- WAS A PUBLICATION FROM DR.  
24 KHORANA'S LAB?

25 A. THAT'S RIGHT, VERY UNUSUAL JOURNAL.