CHEMICAL HERITAGE FOUNDATION

JEFFREY T. HOLT

The Pew Scholars Program in the Biomedical Sciences

Transcript of an Interview
Conducted by

Neil D. Hathaway

at

Vanderbilt University School of Medicine
Nashville, Tennessee

on

3, 4, and 5 January 1993

ACKNOWLEDGEMENT

This oral history is part of a series supported by a grant from the Pew Charitable Trusts based on the Pew Scholars Program in the Biomedical Sciences. This collection is an important resource for the history of biomedicine, recording the life and careers of young, distinguished biomedical scientists and of Pew Biomedical Scholar Advisory Committee members.

From the original collection at the Center for Oral History Research, UCLA Library, UCLA.

The following oral history, originally processed at the UCLA Center for Oral History Research, has been reformatted by the Chemical Heritage Foundation. The process involved reformatting the front matter, adding a new abstract, replacing the table of contents, and replacing the index. The paragraph spacing and font of the body of the transcript were altered to conform to the standards of the Oral History Program at the Chemical Heritage Foundation. The text of the oral history remains unaltered; any inadvertent spelling or factual errors in the original manuscript have not been modified. The reformatted version and digital copies of the interview recordings are housed at the Othmer Library, Chemical Heritage Foundation. The original version and research materials remain at the Darling Library, University of California, Los Angeles and at the Bancroft Library, University of California, Berkeley.

REFORMATTING:

David J. Caruso, Program Manager, Oral History, Chemical Heritage Foundation. B.A., History of Science, Medicine, and Technology, Johns Hopkins University; PhD., Science and Technology Studies, Cornell University.

UNIVERSITY OF CALIFORNIA, LOS ANGELES

Oral History Interview Agreement No. R930127

This Interview Agreement is made and entered into this 29th day of January, 1993, by and between THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, a California corporation, on behalf of the Oral History Program at the UCLA campus, hereinafter called "University," and Jeffrey T. Holt, M.D. having an address at Dept. of Cell Biology, Vanderbilt University School of Medicine, Nashville, TN 37232, hereinafter called "Interviewee."

Interviewee agrees to participate in a series of University-conducted tape-recorded interviews, commencing on or about January 3,1993, and tentatively entitled "Interview with Jeffrey T. Holt, M.D.". This Agreement relates to any and all materials originating from the interviews, namely the tape recordings of the interviews and a written manuscript prepared from the tapes, hereinafter collectively called "the Work."

In consideration of the mutual covenants, conditions, and terms set forth below, the parties hereto hereby agree as follows:

1. Interviewee irrevocably assigns to University all his copyright, title and interest in and to the Work. This assignment applies to University, its successors, and assigns, for and during the existence of the copyright and all renewals and extensions thereof.

2. By virtue of this assignment, University will have the right to use the Work for any research, educational, or other purpose that University may deem appropriate.

3. Interviewee acknowledges that he will receive no remuneration or compensation for his participation in the interviews or for the rights assigned hereunder.

4. Interviewee will receive from University, free of charge, one bound copy of the typewritten manuscript of the interviews.

5. To insure against substantive error or misquotation, Interviewee will have the right to review the manuscript before it is put into final form. University therefore will send Interviewee a copy of the edited transcript for review and comment. Interviewee will return transcript and comments to University within 30 days of receipt of the transcript. In the event that Interviewee does not respond within 30 days, University will assume that Interviewee has given full approval of the transcript.

6. All notices and other official correspondence concerning this Agreement will be sent to the following:

If to University : Office of Intellectual Property Administration
University of California, Los Angeles
405 Hilgard Avenue
Los Angeles, California 90024-1406

Attention: Ms. Carli V. Rogers
Copyright Officer

If to Interviewee: Jeffrey T. Holt, M.D.
Dept. of Cell Biology
Vanderbilt University School of Medicine
Nashville, TN 37232

University and Interviewee have executed this Agreement on the date first written above.

INTERVIEWEE

Jeffrey T. Holt
(Signature)

Jeffrey T. Holt, M.D.
(Typed Name)

Dept. of Cell Biology
(Address)
Vanderbilt University School
of Medicine
Nashville, TN 37232

Date 1/3/92

THE REGENTS OF THE UNIVERSITY
OF CALIFORNIA

Carli V. Rogers
(Signature)

Carli V. Rogers
(Typed Name)

Copyright Officer
(Title)

Date January 29, 1993

Chemical Heritage Foundation
Oral History Program
315 Chestnut Street
Philadelphia, Pennsylvania 19106

JEFFREY T. HOLT

1954 Born in Battle Creek, Michigan, on 24 May

Education

1976 B.A., Health Sciences, Kalamazoo College
1979 M.D., University of Michigan School of Medicine

Professional Experience

University of Rochester, Strong Memorial Hospital
1979-1982 Resident, Pathology
1982-1983 Chief Resident, Clinical Pathology

National Heart, Lung, and Blood Institute, National Institutes of Health
1983-1986 Staff Fellow, Clinical Hematology Branch
1986-1987 Senior Staff Fellow, Clinical Hematology Branch

Vanderbilt University School of Medicine
1987-1991 Assistant professor, Department of Cell Biology and Department of Pathology
1991-present Associate professor, Department of Cell Biology and Department of Pathology

Honors

1975 Phi Beta Kappa
1978 Alpha Omega Alpha, University of Michigan School of Medicine
1988-1992 Scholar, Pew Scholars Program in the Biomedical Sciences
1992-1994 Fogarty Fellowship
1992-present National Cancer Institute Principal Investigator
1992-present Vanderbilt Toxicology National Cancer Institute Cancer Grant

Selected Publications

Holt, J.T. et al., 1982. Elevation of the electronically determined MCV and hematocrit caused by hyperglycemia. *Journal of Clinical Pathology*, 77:56167.
Holt, J.T. et al., 1982. Inhibition of Chromium-51 red blood cell labeling by stannous

pyrophosphate. *Journal of Nuclear Medicine,* 23:934-35.
Holt, J.T. et al., 1982. Spurious macrocytosis caused by hyperglycemia. *American Journal of Clinical Pathology,* 78:572-73.
Holt, J.T. et al., 1983. A technetium-99m red cell survival technique for in vivo compatibility testing. *Transfusion,* 23:148-51.
Holt, J.T. et al., 1983. Spurious macrocytosis caused by osmotic effects. *American Journal of Clinical Pathology,* 79:758-59.
Holt, J.T. et al., 1983. Serum glutamate dehydrogenase in Reye's syndrome: Elevations are masked by enzyme inhibitor. *Lancet,* 2:4-8.
Holt, J.T. et al., 1983. Glutamate dehydrogenase in Reye's syndrome: Evidence for the presence of an altered enzyme in serum with increased susceptibility to inhibition by GTP. *Biochemica et Biophysica Acta,* 749:42-46.
Holt, J.T. et al., 1986. Inducible production of *c-fos* antisense RNA inhibits 3T3 cell proliferation. *Proceedings of the National Academy of Sciences USA,* 83:4793-97.
Holt, J.T. and D.A. Ar^{y}an, 1986. Acute viral hepatitis. In *Clinical Diagnosis and the Laboratory: Logical Strategies for Common Medical Problems,* eds. P.F. Griner, R.J. Panzer, and P. Greenland. Chicago: Yearbook Medical Publisher, 270-83.
Holt, J.T. et al., 1987. Molecular mechanisms of hematopoietic neoplasms. In *The Molecular Basis of Blood Diseases,* eds. G. Stamatoyannopoulos, A.W. Nienhuis, P. Leder, and P. Majerus. Philadelphia: W.B. Saunders, 347-76.
Holt, J.T. and A.W. Nienhuis, 1988. *C-fos* protooncogene expression is necessary for normal growth of mouse 3T3 cells. In *Growth Factors, Tumor Promotors, and Cancer Genes,* eds. N. Colburn, H. Moses, E. Stanbridge. New York: Alan R. Liss, 313-20.
Holt, J.T. et al., 1988. An oligomer complementary to c-myc inhibits proliferation of HL60 promyelocytic cells and induces differentiation. *Molecular Cell Biology,* 8:963-73.
Holt, J.T., 1989. Growth inhibition by antisense nucleic acids. In *Discoveries in Antisense Nucleic Acids,* ed. C. Brakel. Gulf Press, 81-94.
Holt, J.T., 1992. Cutting the chain of command: Specific inhibitors of transcription. *Antisense Research and Development,* 1:365-70.
Holt, J.T., 1992. Antisense promoter mapping: Inhibitory methods of transcriptional analysis. *Annals of the New York Academy of Sciences,* 660:88-95.

ABSTRACT

Jeffrey T. Holt was born and raised in Battle Creek, Michigan—the "Cereal City"—the middle child of three siblings. His father was an electrical engineer who worked for the Kellogg Company in packaging-type machines; his mother was a homemaker. Holt had what he considered a typical childhood, though he developed a great interest in playing piano and then the organ. He won a scholarship to attend the Interlochen Center for the Arts summer camp and was a finalist in the concerto competition; he also decided to play the organ for his church. Norman Rubell, a high school biology teacher who taught using the Socratic method, proved to be quite influential.

He attended Kalamazoo College in Michigan, in part because it was close to his home, intending to pursue both music and premed majors, though he ultimately gave up music. Kalamazoo did not provide any opportunities for laboratory research. Following (somewhat) in his brother's footsteps, Holt went on to matriculate at the University of Michigan to pursue his medical doctorate. After completing medical school he went on to his residency in pathology at the Strong Memorial Hospital at the University of Rochester, before beginning postdoctoral work in the Arthur W. Nienhuis lab at the National Heart, Lung, and Blood Institute in Bethesda, Maryland, studying globin mRNA in thalassemia and investigating the effects of antisense *fos*Some of the research in the Nienhuis lab was stymied due to leakage from the Xenopus oocyte nuclei which undermined transport experiments. From there he went on to a faculty position in the Departments of Cell Biology and of Pathology at the Vanderbilt University School of Medicine.

Throughout the interview Holt talks about the ways in which the practice of medicine differs from research, applying insights in pathology to cancer research, and the difficulties in applying molecular biology cancer research in practice. He also discusses how the antisense field gained acceptance and his application for a patent on a topical antisense delivery system. The interview concludes with his thoughts on applying *fos* antisense research to human cancer; searching for transcriptional differences between *c-fos* and v-*fos*; Marilyn D. Resh's study of reticulocyte lysates and myrisylation; and Inder M. Verma's mapping of the *fos* phosphorylation site. Holt ends the interview with reflections on his decision not to patent his HL60 leukemia cell antisense; marketing basic science research to the public; and the need to try risky experiments.

UCLA INTERVIEW HISTORY

INTERVIEWER:

Neil D. Hathaway, Interviewer, UCLA Oral History Program. B.A., English and History, Georgetown University; M.A. and C.Phil., History, UCLA.

TIME AND SETTING OF INTERVIEW:

Place: Holt's office, Vanderbilt University School of Medicine.

Dates, length of sessions: January 3, 1993 (59 minutes); January 4, 1993 (119); January 5, 1993 (153).

Total number of recorded hours: 5.5

Persons present during interview: Holt and Hathaway.

CONDUCT OF INTERVIEW:

This interview is one in a series with Pew scholars in the biomedical sciences conducted by the UCLA Oral History Program in conjunction with the Pew Charitable Trusts's Pew Scholars in the Biomedical Sciences Oral History and Archives Project. The Project has been designed to document the backgrounds, education, and research of biomedical scientists awarded four-year Pew scholarships, from 1988 through 1992.

In preparing for this interview, Hathaway, in consultation with the director of the UCLA Oral History Program and three UCLA faculty project consultants, developed a topic outline to provide an overall interview framework. Hathaway then held a telephone preinterview conversation with Holt to obtain extensive written background information (curriculum vitae, copies of published articles, etc.) and agree on a research and interviewing timetable. Hathaway further reviewed the documentation in Holt's file at the Pew Scholars Program office in San Francisco, including his proposal application, letters of recommendation, and reviews by Pew Scholars Program national advisory committee members. For general background on the recent history of the biological sciences, Hathaway consulted such works as: J.D. Watson et al., *The Molecular Biology of the Gene.* 4th ed. 2 vols. Menlo Park, CA: Benjamin/Cummings, 1987; Lubert Stryer, *Biochemistry.* 3d ed. New York: W.H. Freeman, 1988; *The Journal of the History of Biology;* H.F. Judson, *The Eighth* Day of *Creation: Makers of the Revolution in Biology. New* York: Simon and Schuster, 1979; and current issues of *Science, Nature,* and *Cell.*

The interview is organized chronologically, beginning with Holt's childhood and education in Battle CreekMichigan, and continuing on to his medical education at the University of Michigan School of Medicine, residency at the University of Rochester, fellowship at the National Heart, Lung, and Blood Institute, and subsequent career at the Vanderbilt University School of Medicine. Major topics discussed include Holt's specialization in pathology, his training as a physician-scientist, the comparative study of oncogenes in mice and humans, research on antisense *fos* gene, his application for a patent for a topical antisense delivery

system, and strategies for cancer research.

ORIGINAL EDITING:

Steven J. Novak, senior editor, edited the interview. He checked the verbatim transcript of the interview against the original tape recordings, edited for punctuation, paragraphing, and spelling, and verified proper names. Words and phrases inserted by the editor have been bracketed.

Holt reviewed the transcript. He verified proper names and made minor corrections.

Novak also prepared the table of contents, biographical summary, interview history, and index.

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