Human Chromosomes and Cancer: Tumors and the Geographies of Cytogenetic Practices, 1951–1956

ABSTRACT

In this paper I analyze the trajectory of research objects and experiments on tumor cells that led the Swedish geneticist, Albert Levan, through successive collaborations with Theodore Hauschka in Philadelphia (U.S.) and Joe Hin Tjio in Lund (Sweden), from plants to mice and from mice to human chromosomes. Tumor chromosomes were created and recreated in mice bodies by Eva Klein and Georg Klein as ascites–fluid–tumors, whereas human tumors were transplanted from the bodies of cancer patients into mice by Helene W. Toolan. The cultures of cytogenetics and microscopic observation were therefore opened up, from agricultural and botanical research to the clinical laboratory. I suggest it was research on tumors and cancer cells that led to a method for obtaining clear slides, thereby providing evidence of the new number of forty-six human chromosomes, as presented by Tjio and Levan in 1956. Along this research trajectory, the knowledge and practices of cytogenetics were medicalized—a medicalization that situated both cancer research and cytogenetics at the origins of biomedicine.

KEY WORDS: Albert Levan, Joe Hin Tjio, Theodore Hauschka, Eva Klein, George Klein, Helene W. Toolan, human cytogenetics, polyploidy

In December 1951, at the meeting of the American Association for the Advancement of Science, zoologist Theodore Hauschka, from the Institute of Cancer Research in Philadelphia, and Swedish cytologist Albert Levan, from the Institute of Genetics in Lund, Sweden, reported a characterization of seven tumors

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The following abbreviations are used: *CR*, *Cancer Research*; *JHB*, *Journal of the History of Biology*; Levan Papers, Universitetsbiblioteket, Lunds Universitet [Lund University Library], Lund, Sweden.

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in mice, among them lymphomas, carcinomas, and sarcomas. In the set of sixteen slides, they showed chromosomes of cancerous cells during division. Cancer chromosome numbers were unusually high, and were represented as polyploids of the normal set.¹

The number of chromosomes in cells with the polyploidy effect is a multiple of the normal number. This phenomenon was first observed in plants by Anne May Lutz at the newly created Cold Spring Harbor Station for Experimental Evolution in 1907.² Some species were regarded as natural polyploid varieties of others, but there were also chemically induced varieties of a larger size with double chromosome numbers, produced by the action of compounds such as colchicine.³

Hauschka and Levan were studying experimental cancer in mice, by using mouse ascites tumors obtained by a technique recently established by Eva and Georg Klein. These nonsolid tumors—ascites—grew in the peritoneal cavity of certain hybrid mice and, being easier to handle than tissues, were regarded as extremely valuable material for investigating the growth of neoplastic cells and for cytological observation.⁴ Some of these tumor cells under study functioned as stem cells: they divided constantly and freely to produce a “typical ascites

1. Theodore Hauschka and Albert Levan, “Characterization of Seven Ascites Tumours with Respect to Chromosome Ploidy and Histocompatibility,” handwritten at the top: “This will not be published and is simply text of my 10 minute AAAS talk, Dec 28, 1951,” undated. Levan Papers, Folder Levan-Hauschka correspondence, 1951–1956. On the AAAS meeting that year, see “Preview of the 118th Meeting, AAAS, Philadelphia December 26–31, 1951,” *Science* 114 (1951): 593–620.

2. Marsha Richmond, “Women in Mutation Studies: The Role of Gender in the Methods, Practices and Results of Early Twentieth-Century Genetics,” in *Making Mutations: Objects, Practices and Contexts*, ed. Luis Campos and Alexander von Schwering (Berlin: Max Planck Institut für Wissenschaftsgeschichte, 2010), 11–47.

3. For a history of colchicine, including its early uses in the treatment of gout, its well-known intense toxicity, and its activity in increasing blood cell counts, see Jordan Goodman, “Plants, Cells and Bodies: The Molecular Biography of Colchicine, 1930–1975,” in *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s–1970s*, ed. Soraya de Chadarevian and Harmke Kamminga (Amsterdam: Harwood, 1998); and Helen A. Curry, “Accelerating Evolution, Engineering Life: American Agriculture and Technologies of Genetic Modification, 1925–1960” (PhD dissertation, Yale University, 2012).

4. On cancer tissues, see Tricia Close-Koenig, “Histopathology Slides from Medical Research to Medical Practice in Interwar Strasbourg,” *History and Philosophy of the Life Sciences* 35 (2013): 341–61; Georg Klein and Eva Klein, “The Transformation of a Solid Transplantable Mouse Carcinoma into an ‘Ascites’ Tumour,” *CR* 11 (1951): 466–69. By then colchicine was also being tested as a treatment against cancer; see J. W. Cook and J. D. Loudon, “Colchicine,” in *The Alkaloids: Chemistry and Physiology*, vol. 2, ed. R.H.F. Manske and H. L. Holmes (New York: Academic Press 1952), 261–329.

FIG. 1. Chromosomes of ascites tumors in mice. *Source:* Albert Levan and Theodore S. Hauschka, "Endomitotic Reduplication Mechanisms in Ascites Tumors of the Mouse," *Journal of the National Cancer Institute* 14 (1953): 1–43, on 23. Reprinted with permission.

tumour" which, it was determined, propagated malignancy while keeping high chromosome numbers over successive generations (Fig. 1).⁵

Four years later, by late 1955, Levan and Indonesian cytogeneticist Joe Hin Tjio obtained a set of slides of forty-six human chromosomes, presumably in healthy, noncancerous cells, while working at the Institute of Genetics of the University of Lund (Fig. 2).⁶ Until this discovery, the accepted number of the human chromosome set had been forty-eight. It was the method of preparation that made the determination of the new number possible, producing clear slides in which chromosomes appeared separated, enabling a reliable count.⁷

In this paper I analyze the trajectory of experiments and research objects that led Albert Levan, through successive collaborations with Hauschka and Tjio, from plants to mice and from mice to human cells. This transference of

5. Theodore S. Hauschka and Albert Levan, "Progress report for grant C-1663: Studies on the maintenance of chromosomal (ploidy) differences between populations of ascites tumour cells," undated, ca. December 1951, Levan Papers. Hauschka and Levan worked together at the Institute in Philadelphia, previously located at the Lankenau Hospital. Early contact between the two of them could have occurred at the Karolinska Institute and the Wallenberg Foundation, which had formerly funded the unit of cytogenetics at Svalöf. Caspersson was in touch with Jack Schultz from the 1930s; they published together. See George Klein and Eva Klein, "How One Thing Has Led to Another," *Annual Review of Immunology* 7 (1989): 1–33; on Schultz, see Thomas F. Anderson, "Jack Schultz 1904–1971," *Biographical Memoir National Academy of Sciences* (1975): 391–422; on Klein's view of Caspersson, see George Klein and Eva Klein, "Torbjörn Caspersson," *Proceedings of the American Philosophical Society* 147 (2003): 73–75.

6. Joe Hin Tjio and Albert Levan, "The Chromosome Number of Man," *Hereditas* 42 (1956): 1–6.

7. See de Chadarevian, this Issue. On counting, see Aryn Martin, "Can't Any Body Count? Counting as an Epistemic Theme in the History of Human Chromosomes," *Social Studies of Science* 34 (2004): 923–48. Malcom Kottler, "From Forty-Eight to Forty-Six: Cytological Technique, Preconception and the Counting of the Human Chromosomes," *Bulletin of the History of Medicine* 48 (1974): 465–502.

FIG. 2. Human embryonic chromosomes from lung fibroblase. *Source:* Tjio and Levan, "Chromosome Number of Man" (ref. 6), 4. Reprinted with permission.

cancer as an experimental event studied successively in plants, mice, and then in human tumors was guided by polyploidy, as a research subject produced in cancer tumors that contained unusually high chromosome numbers. Cancer, which had been a visible scientific disease for over half a century, was a biological as well as a medical issue, the process of tumor formation through the unlimited multiplication of cells not being fully understood. The shift from agricultural and botanical research to the clinical laboratory opened up the cultures of cytogenetics and microscopic observation, making chromosomes visible in slides under the microscope.⁸

A network composed of Levan, Hauschka, Tjio, the Kleins, and Helene W. Toolan and her collaborators participated with others in producing research that linked polyploidy cells with cancer. A method for obtaining clear slides of normal human cells was established through the close collaboration of Levan and Tjio, at a time when Levan was beginning to study human tumor cells. The techniques for culturing human tumors in mice, in which Levan was

8. On experimental arrangements and technologies of visualization, see Angela N. H. Creager and Jean-Paul Gaudillière, "Experimental Platforms and Technologies of Visualization: Cancer as Viral Epidemic, 1930–1960," in *Heredity and Infection: The History of Disease Transmission*, ed. Jean-Paul Gaudillière and Ilana Löwy (London: Routledge, 2001), 203–41.

being trained, had been devised by Helene W. Toolan, a pathology researcher at the Sloan-Kettering Institute for Cancer Research in New York.⁹

In this trajectory, Levan's plant cytology expertise combined with both a long-standing interest in biological experimentation on cancer cells, and the promotion of cancer research as part of the postwar U.S. research policy into the effects and uses of radiation. The set of events studied in this paper took place during the expansion of funding for cancer research in the United States, as a collective endeavor in which fundraisers, political authorities, and individual scientists contributed to the development of contemporary Western biomedicine.¹⁰ Cytogenetics, chromosomes, and cancer cells combined to give rise to human cytogenetics, which would later become a diagnostic tool in the clinic for different medical purposes and associated with different disorders.¹¹ Here I will focus on the development of a technique for making visible the chromosomes of human tumor cells. Many skills and research agendas converge in my reconstruction. These research projects, intertwined in my paper, were focused on cancer cell growth and on the size and shape of tumor cell chromosomes as representations of cancer. This essay situates cancer

9. Helene W. Toolan, "Transplantable Human Neoplasms Maintained in Cortisone Treated Laboratory Animals: H.S. #1; H.Ep. #1; H.Ep. #2; H.Ep. #3; and H.Emb.Rh. #1*t," *CR* 14 (1954): 660–66. On Levan's visit to the SKL, see Levan to Hauschka, 28 Mar 1955; Levan to Hauschka, 10 May 1955; Levan to Toolan, 21 Sep 1955, all in Levan Papers.

10. On cancer and biomedicine, see Jean-Paul Gaudillière, "Cancer," in *The Cambridge History of Science, Vol. 6, The Modern Biological and Earth Sciences*, ed. Peter J. Bowler and John V. Pickstone (Cambridge-New York: Cambridge University Press, 2009), 486–503; and Ilana Löwy, "Cancer: The Century of the Transformed Cell," in *Science in the Twentieth Century*, ed. John Krige and Dominique Pestre (Amsterdam: Harwood Academic, 1997), 461–77.

11. Daniel J. Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity* (Berkeley: University of California Press, 1985); M. Susan Lindee, *Moments of Truth in Genetic Medicine* (Baltimore, MD: Johns Hopkins University Press, 2005); Vassiliki B. Smocovitis, "Genetics Behind Barbed Wire: Masuo Kodani, Émigré Geneticists, and Wartime Genetics Research at Manzanar Relocation Center, 1942–1945," *Genetics* 187 (2011): 357–66; Nathan Comfort, *The Science of Human Perfection: How Genes Became the Heart of American Medicine* (New Haven, CT: Yale University Press, 2012); Peter S. Harper, *First Years of Human Chromosomes: The Beginnings of Human Cytogenetics* (Bloxham [Great Britain]: Scion, 2006); see also María Jesús Santesmases, "Cereals, Chromosomes and Colchicine: Crop Varieties and Human Cytogenetics at the Estación Experimental Aula Dei, 1948–1958," in *Human Heredity in the 20th Century*, ed. Bern Gausemaier, Staffan Müller-Wille, and Alexander von Schwerin (London: Pickering and Chatto, 2013), 127–40; María Jesús Santesmases, "The Autonomous Karyotype and the Origins of Prenatal Testing: Children, Pregnant Women and Early Down Syndrome Cytogenetics, Madrid 1962–1975," *Studies in History and Philosophy of Biological and Biomedical Sciences* 47 (2014): 142–53. For a case of early medical genetics, see the one on Mexico in Barahona, this Issue.

chromosomes at the origin of the new number of human chromosomes—forty-six instead of the previously accepted forty-eight—evident after 1956. Through the subsequent development of cytogenetics in medical diagnosis, the biological knowledge and practices of cytogenetics were medicalized.¹² Mutation as a cancerous phenomenon was linked to Cold War science policy through the increasing funding provided in the United States for radiation biology and cancer research.¹³ Throughout the story, cancer situates itself at the origins of biomedicine, as tumor cell chromosomes situated the early days of human cytogenetics during the postwar within clinical knowledge and practices.

The story unfolds in three parts. After briefly introducing the issue of cancer and tumor cytology, I will analyze in the first part Levan's research into polyploidy, the development of his expertise in studying plant chromosomes and his introduction to the concept of tumors in plant roots when polyploidy was detected while keeping drawings as evidence. In the second part, I present Levan's shift to mice tumors and his collaboration with Theodore Hauschka at the Institute for Cancer Research in Philadelphia. I then move on with Levan to the problem of human tumors and the techniques that were, by then, starting to be used to study them—through the introduction of human tumors to mice bodies, using methods described at the time by Helene W. Toolan.

This series of techniques became, as a set, the epistemic object constructed by taking elements from different living things. Such series evolved over time with the living object at hand: experimental bodies being plant cells, mice cells, human cells in mice and, finally, isolated cultured human cells. Superimposed chemicals and biologicals created new objects—slides—that carried new meanings and opened the pathway for further techniques. This set contributed to the characterization not only of cancer cells and their growth but of a new number of human chromosomes. The entire landscape of experiments, and the

12. See Alberto Cambrosio, Peter Keating, Thomas Schlich, and Georg Weisz, "Regulatory Objectivity and the Generation and Management of Evidence in Medicine," *Social Science and Medicine* 63 (2006), 189–99. On the origins of biomedicine, see also Soraya de Chadarevian and Harmke Kamminga, "Introduction," in *Molecularizing Biology and Medicine: New Practices and Alliances, 1920s to 1970s* (London: Taylor & Francis, 1998).

13. See Creager, this Issue. On biology and medicine as disciplines directly benefitting from the cultures and policies of the Cold War Atomic age, see the arguments on biophysics in Nicolas Rasmussen, "The Mid-Century Biophysics Bubble: Hiroshima and the Biological Revolution in America, Revisited," *History of Science* 35 (1997): 245–93.

products of such experiments, illustrates the early biomedical domain as a scientific culture based on cytogenetic images.¹⁴

POLYPLOIDY AS TUMORS IN PLANTS

By mid-century, species with high numbers of chromosomes were well known to geneticists, botanists, and plant biologists, who studied them through cytological observation. In 1907, Anne May Lutz had produced a hybrid evening primrose (*Oenothera*) at the Cold Spring Harbor Station for Experimental Evolution (New York), which had double and quadruple numbers of chromosomes, leading Lutz and her contemporaries to talk of triploid and tetraploid mutants in the *Oenothera*. Plant cytology had become a competitive field of study, and polyploidy, as Marsha Richmond has phrased it, one of its most intriguing subjects.¹⁵

The majority of plants in which a chromosome number had been determined were polyploids. British botanist Cyril Darlington presented examples of wheat. Its diploid form, the one with what he called a “basic” number of chromosomes, was *Triticum monococcum* (small spelt wheat). Among its polyploids, he mentioned *T. dicoccum* (emmer wheat), *T. turgidum* (river wheat), *T. durum* (macaroni wheat), and *T. virginiana* (spiderwort) as tetraploids, that is, wheats with double the chromosomes; and *T. vulgare* (bread wheat) and *T. spelta* (spelt wheat) as hexaploids, with triple the number of chromosomes.¹⁶

Polyploidy and cancer had their own genealogical links. The consequences of induced polyploidy through the action of the alkaloid colchicine had been observed in 1937, in cancerous tumors in animals at the pathology laboratory of

14. On the circulation of the products of genetic experimentation, i.e., wheat seed, see Tiago Saraiva, “Fascist Landscapes: Geneticists, Wheat, and the Landscapes of Fascism in Italy and Portugal,” *HSNS* 40 (2010): 457–98. Saraiva focuses on the historical developments of two fascist regimes, but it is his reflection on the circulation of seeds that relates to the focal point of my paper. See also Robert E. Kohler, “Practice and Place in Twentieth-Century Field Biology: A Comment,” *JHB* 45 (2012): 579–86, where the concept of circulation is discussed by giving agency to “place” and “site.”

15. Richmond, “Women in Mutation Studies” (ref. 2), 20.

16. I briefly discuss polyploidy as a biological phenomena in Maria Jesús Santesmases, “The Biological Landscape of Polyploidy: Chromosomes Under Glass in the 1950s,” *History and Philosophy of the Life Sciences* 35 (2013): 91–97. Original sources for this are cited by Cyril Darlington, *Chromosome and Plant Breeding* (London: Macmillan and Co., 1932), 72–82. On Darlington, see Oren S. Harman, *The Man Who Invented the Chromosomes* (Cambridge, MA: Harvard University Press, 2004).

the University of Brussels, headed by Albert Pierre Dustin. E. C. Amoroso also tested colchicine in tumors in 1935, demonstrating inhibition of tumor growth, and in 1937 at the department of genetics in Cold Spring Harbor, Albert Blakeslee's experiments with colchicine produced Jimson weed *Datura* species of a larger size than normal and with double the number of chromosomes (tetraploids). By the late 1930s, Cold Spring Harbor was a laboratory of genetics at which breeding and evolution studies were carried out. Although polyploidy had been detected in wild species far earlier, the treatment of plants with colchicine was the first artificial method—through the action of a chemical compound—for obtaining polyploid varieties.¹⁷ The effect of colchicine was usually an increase in the size of plant parts: leaves, stem, branches, flower parts, fruits and seeds.¹⁸

From the late 1930s onward, genetics was coming to be seen as an intersection of breeding and cytology. Early cytogeneticists were botanists studying the chromosomal preparations they themselves had produced, looking through the microscope at the cell within and creating, as Rheinberger has called it, “a world of artifacts under glass,” literally *in vitro*.¹⁹ One of the places where plant polyploidy was intensively studied from that time forward was the Swedish Seed Association's experimental station in Svalöf, Sweden, where Albert Levan started his research as a plant biologist in the late 1920s.²⁰

17. Colchicine, the alkaloid that produced artificial polyploidy in plants, was a product extracted from meadow saffron colchicum, the effect of which on gout had been known for centuries. Its poisonous effect was also compatible with its action as a mitosis promoter and polyploidy generator. On colchicine, see Jordan Goodman, “Plants, cells and bodies” (ref. 3); Helen A. Curry, “Making Marigolds: Colchicine, Mutation Breeding, and Ornamental Agriculture,” in *Making Mutations: Objects, Practices and Contexts*, ed. Luis Campos and Alexander von Schwering (Berlin: Max Planck Institut für Wissenschaftsgeschichte, 2010), 259–83; Curry, “Accelerating Evolution, Engineering Life” (ref. 3). On the origins of polyploidy, see Richmond, “Women in Mutation Studies” (ref. 2). See also Albert Levan, “The Effect of Colchicine in Root Mitosis in Allium,” *Hereditas* 24 (1938): 471–86. The original results of Blakeslee are in Albert F. Blakeslee and Amos G. Avery, “Methods of Inducing Doubling of Chromosomes in Plants by Treatment with Colchicines,” *Journal of Heredity* 28 (1927): 393–411. On Blakeslee, see Barbara A. Kimmelman, “Mr. Blakeslee Builds His Dream House: Agricultural Institutions, Genetics, and Careers 1900–1915,” *JHB* 39 (2006): 241–80; Luis Campos, “Genetics Without Genes: Blakeslee, *Datura*, and ‘Chromosomal Mutations’,” in *A Cultural History of Heredity, V: Heredity in the Century of the Gene* (Berlin: Max Planck Institute for the History of Science, 2008), 243–57.

18. See Levan, “Effect of Colchicines” (ref. 17).

19. Hans-Jörg Rheinberger, *An Epistemology of the Concrete* (Durham and London: Duke University Press), 238–240.

20. On Svalöf, see Staffan Müller-Wille and Christian Bonneuil, “Trials and Registers: The Archives of Svalöf Weibull and Vilmorin Companies,” *Mendel Newsletter* 16 (2007): 16–21;

Levan's work on the plant cytology of *Allium*, the onion genus, began in 1929. Following his visit to genetics laboratories in the United States in 1937, where he carried out colchicine studies with B. R. Nebel at the New York State Agronomic Experimental Station, Levan began research into the effects of colchicine on chromosomes. Back in Sweden in 1938, he carried out research on polyploidy and colchicine mitosis.²¹

In 1935, Levan was assistant professor of genetics at the University of Lund. From 1933 until 1938, he was first assistant at the Swedish Sugar Beet Company, and from 1939 until 1947, head of the Cytological Unit of the Swedish Seed Association at Svalöf. Levan was a researcher at the University of Lund Institute of Genetics from the beginning of 1947 until 1961, when he was awarded a full professorship after a long research career in plant and animal genetics.²²

By 1929, Levan had obtained clear drawings of onion chromosomes with the use of a camera lucida.²³ The large size and clear shapes he was able to obtain led him to consider *Allium* a useful plant for studying the effects of exposure to chemicals and radiation. As Anne May Lutz had in the early twentieth century, Levan used the root-tips of the plant, a source that enabled clear images of chromosomes to be seen through a microscope—a process he called the *Allium* test.²⁴ From that time forward, onion chromosomes became a reference point in his research. He designed a method for clearly observing *Allium* chromosomes on the slides and was skilled at drawing. Chemical compounds caused these chromosomes to break into parts and multiply, increasing plant size. Through the creation of polyploidy in *Allium*, chromosome experiments were

Staffan Müller-Wille, "Hybrids, Pure Cultures and Pure Lines: From Nineteenth Century Biology to Twentieth Century Genetics," *Studies in History and Philosophy of Biological and Biomedical Sciences* 38 (2007): 796–806.

21. Levan, "Effect of Colchicines" (ref. 17); Albert Levan, "Note on the Somatic Chromosomes of Some Colchicum Species," *Hereditas* 26 (1940): 317–20. See also J. Eigsti and Pierre Dustin Jr., *Colchicine in Agriculture, Medicine, Biology and Chemistry* (Ames: Iowa State College Press, 1955), 21. From 1939, Levan headed the cytogenetics department of the Seeds Experimental Station in Svalöf. On Svalöf standing out as an experimental station where polyploidy was among its expertise, see Müller-Wille, "Hybrids, Pure Cultures" (ref. 20).

22. Maj A. Hultén and Karl Fregda, "Albert Levan," in *Nature Encyclopedia of the Human Genome* (London: Macmillan, 2003), 688–89.

23. Albert Levan, "Zahl und Anordnung der Chromosomen in der Meiosis von Allium," *Hereditas* 13 (1929): 80–87.

24. Albert Levan, "Cytological Studies in Allium II: Chromosome Morphological Contributions," *Hereditas* 16 (1932): 257–95, and Hultén and Fregda "Levan" (ref. 22).

FIG. 3. Chromosomes of *Allium* varieties, before Levan began to use colchicine. *Source:* Levan, "Cytological Studies in *Allium* II" (ref. 24), 263 (b, c, d). Reprinted with permission.

FIG. 4. Mitosis in *Allium* under the action of colchicine. *Source:* Levan, "Effect of Colchicine" (ref. 17), 473. Reprinted with permission.

performed: forms and numbers emerged during a process that connected chromosomes with the anatomy of the plant (Figs. 3 and 4).

Following previous research on the relationship between colchicine and polyploidy, Levan investigated the mitotic deviation induced by colchicine by exposing the root cells of the plant to different concentrations and different

exposure times, and studying the resulting mitosis.²⁵ He was able to show the formation of tumors produced by the action of colchicine, and how, after some rest, the plant could recover and produce normal cells again with the usual chromosome numbers. "The tumours take the shape of a string of pearls," he stated.²⁶ He continued this research for roughly a decade, systematically testing *Allium* root cells and other plants, including rye and mimosa, under the action of many chemicals. In 1949, Levan and Thoraya Lofty checked the growth of plant roots through the application of colchicine and acetylnaphthalene.²⁷

The action of the polyploidy agent colchicine was the production of cells expanding equally in all directions, known as c-tumors. The onion and its roots grew in size when treated with the set of chemicals, from colchicine to penicillin, used by Levan and his colleagues.²⁸

CANCER AND HEREDITY: CYTOLOGY BEFORE AND AFTER WORLD WAR II

Unusual chromosome numbers had been associated with cancer cells for decades, cancer cells having been studied using cytological methods since the late nineteenth century. German cytologist and experimental zoologist Theodore Boveri had referred to the asymmetrical division of cancer cells when describing mitotic irregularity and the lack of cellular organization into a differentiated tissue. He inferred a causal relationship, noting the lack of tissue organization in tumorous growth. In his *Chromosome Theory of Cancer* (1914), Boveri stated that malignant growth originated in somatic cells that had acquired an abnormal chromosome content as a result of an "asymmetrical" mitosis. Later, Øjvind Winge, from the Carlsberg Laboratory, provided the cytological

25. For a review on the knowledge then available about colchicine, and its relation to polyploidy and cancer, already suggested by some researchers, see J. W. Cook and J. D. Loudon, "Colchicine" (ref. 4), esp. 291–317.

26. Levan, "Effect of Colchicines" (ref. 17). On the term "c-mitosis," see Levan's own discussion of its meaning and uses in Albert Levan, "Colchicine Induced C-Mitosis in Two Mouse Ascites Tumours," *Hereditas* 40 (1954): 1–64, on 50–51.

27. Albert Levan and Thoraya Lofty, "Naphthalene Acetic Acid in the Allium Test," *Hereditas* 35 (1949): 337–74.

28. Albert Levan and Joe Hin Tjio, "Induction of Chromosome Fragmentation by Phenols," *Hereditas* 34 (1948): 453–85; Albert Levan and Joe Hin Tjio, "Penicillin in the Allium Test," *Hereditas* 37 (1951): 306–24.

evidence for Boveri's proposal: in both plant and animal tumors, many cells contained an abnormal number of chromosomes, a large proportion having twice the number of chromosomes found in normal cells, which was regarded a feature of most malignant cells.²⁹

Levan and Hauschka studied the cytology of transplanted tumors, utilizing the transplantation technique recently invented by Georg and Eva Klein. The Kleins developed a method for producing ascites tumors in the peritoneal cavity of mice after inoculating a solid tumor.³⁰ Whereas the Kleins, who collaborated with Torbjörn Caspersson at the Karolinska Institute in Stockholm, were interested in the contents of nucleic acids, Hauschka and Levan concentrated on the association between unusual chromosome numbers and polyploidy. It became apparent to Levan and Hauschka that the enlarged size of tumors (and of tumor cells) derived from unusually high numbers of chromosomes, and that this unusually high number came about during cell division. They accepted the proposal, made separately by Boveri and Winge, that malignant cells were produced by this mechanism and that malignancy propagated over successive generations of cells.

Following World War II, research into the genetic and congenital effects of radiation was promoted, and chromosomes became an intriguing subject in biological research on cancer. The global prominence of U.S. radiobiology research and the creation of the Atomic Energy Commission attracted researchers at a time when Europe was still recovering from the devastation of the war.³¹ By that time, researchers understood cancer as both a product of radiation and a set of diseases for which radiation held therapeutic promise,

29. Theodore Boveri, *Zur Frage der Entstehung maligner Tumouren* (Jena: Gustav Fischer, 1914). It was translated into English by Boveri's wife, Marcella O'Grady Boveri, after her husband died, and published in 1929 in Baltimore as *Chromosome Theory of Cancer*, which contributed to the construction of Boveri's reputation in the United States. See the reconstruction by Peo C. Koller in *The Role of Chromosome in Cancer Biology* (New York: Springer Verlag, 1972), chap. 3. On the Boveris, see Helga Satzinger, "Theodor and Marcella Boveri: Chromosomes and Cytoplasm in Heredity and Development," *Nature Review Genetics* 9 (2008): 231–38; and Victor A. McKusick, "Marcella O'Grady Boveri (1865–1959) and the Chromosome Theory of Cancer," *Journal of Medical Genetics* 22 (1985): 431–40. On Winge, see Anonymous, "Professor Øjvind Winge, [who] celebrates his 70th anniversary," *Hereditas* 42 (1956): unpaginated.

30. The early papers by the Kleins include Eva Klein, N. B. Kurnick, and Georg Klein, "The Effect of Storage on the Nucleic Acid Content and Virulence of Mouse Ascite Tumours," *Experimental Cell Research* 1 (1950): 127–34. Also Klein and Klein, "The Transformation of a Solid Transplantable Mouse Carcinoma" (ref. 4); Eva Klein and Georg Klein, "Differential Survival of Solid Tumour Cells after Inoculation into Established Ascites Tumours," *CR* 14 (1954): 139–44.

31. Rasmussen, "Mid-Century Biophysics Bubble" (ref. 13); Creager, this Issue.

just as X-rays had.³² Both cancer and genetics could be pursued at the chromosomal level, being supported, promoted, and funded by post-WWII policies for developing civilian uses of atomic energy.³³ Cancer as an effect of either radiation or mutations, or both, was under study in an experimental space where pathology and cytogenetics converged—or more specifically, where pathology underwent *geneticization*.³⁴ In this context, the chromosomal studies of Hauschka and Levan contributed to the basis of cancer genetics and medicalized cytogenetics. As a biological technology, cytogenetics became involved in research into cancer as a medical problem.

At the same time that Charles Ford and John Hamerton were conducting genetic research at the British government's atomic energy installation in Harwell, U.S. geneticists were using inbred mice to study radiation-induced mutations at Oak Ridge.³⁵ In the post-WWII era, as some authors have noted, the atomic dimension of genetics underwent a change in scale.³⁶ Cytologists

32. Gaudillière, "Cancer" (ref. 10); Ilana Löwy, *Between Bench and Bedside: Science, Healing, and Interleukin-2 in a Cancer Ward* (Cambridge, MA: Harvard University Press, 1996). On cancer, see also David Cantor, "Introduction: Cancer Control and Prevention in the Twentieth Century," *Bulletin for the History of Medicine* 81 (2007): 1–38. On genetics and radiation, see M. Susan Lindee, *Suffering Made Real: American Science and the Survivors at Hiroshima* (Chicago: University of Chicago Press 2008); John Beatty, "Scientific Collaboration, Internationalism, and Diplomacy: The Case of the Atomic Bomb Casualty Commission," *JHB* 26 (1993), 205–31; Soraya de Chadarevian, "Mice and the Reactor: the 'Genetic Experiment' in Genetics in Britain," *JHB* 39 (2006): 707–35.

33. See Creager, this Issue. On biology and medicine as disciplines benefitting from the cultures and policies of the atomic age, see Soraya de Chadarevian, "Putting Human Genetics on a Solid Basis: Human Chromosome Research, 1950s–1970s," in *Human Heredity in the Twentieth Century*, ed. Bernd Gausemeier, Staffan Müller-Wille, and Edmund Ramsden (London: Pickering & Chatto, 2013), 141–51; also Rasmussen, "Mid-Century Biophysics Bubble" (ref. 13). On the civilization of atomic energy, see Angela Creager, *Life Atomic: A History of Radioisotopes in Science and Medicine* (Chicago: University of Chicago Press, 2013); Angela Creager and Maria J. Santesmases, "Radiobiology in the Atomic Age: Changing Research Practices and Policies in Comparative Perspective," *JHB* 39 (2006): 637–47; John Krige, "The Peaceful Atom as a Political Weapon: Euratom and American Foreign Policy of the 1950s," *HSNS* 38, no. 1 (2008): 5–44; María Jesús Santesmases, "Peace Propaganda and Biomedical Experimentation: Radioisotopes in Endocrinology and Molecular Genetics, and Their Influence in Spain (1950–1971)," *JHB* 39 (2006): 765–98.

34. On the diagnosis of cancer by tissue analyses, see Ilana Löwy, *Preventive Strikes* (Baltimore, MD: Johns Hopkins University Press, 2010), 29–32.

35. De Chadarevian, "Mice and the Reactor" (ref. 32); Karen Rader, *Making Mice: Standardizing Animals for American Biomedical Research, 1900–1955* (Princeton, NJ: Princeton University Press, 2004), 180–96.

36. See note 32.

were able to make visible the innermost part of the cell—the chromosomes—displacing, at least temporarily, the centrality of the tissue in pathology; even though tissue observation would remain one of the analytical tools for cancer diagnosis. From this hybridization of practices—pathology and cytogenetics interacting—Levan and Hauschka established the differences between the normal diploid chromosomes number of the mouse (forty), and the chromosome number of its malignant tumor cells.

Cancer as Polyploidy in Mice

While continuing his research agenda on plant chromosomes in Lund, Levan travelled to the United States in 1951. He was invited by the director of the Cold Spring Harbor Biological Laboratory, Milislav Demerec, to give a talk at the XVI Cold Spring Harbor Symposium on Genes and Mutations. Levan was expected to contribute to the session on Induction of Changes in Genes and Chromosomes. He also planned to visit other U.S. laboratories where the chemical treatment of chromosomes was being researched. Before the symposium he went to see Jack Schultz at the Institute for Cancer Research in Philadelphia.³⁷ Schultz, a *Drosophila* geneticist, invited Georg Klein at the Cell Research Department of the Karolinska Institute in Stockholm to instruct him and Theodore Hauschka on working with ascites tumors. Klein's visit was paid for by the Knut and Alice Wallenberg Foundation, which in 1931 had funded the creation of the cytogenetics department at the Svalöf Agronomy Station and the cell department at the Karolinska Institute, headed by Torbjörn Caspersson.³⁸ Shortly thereafter, Swedish cytologist Albert Levan joined the group and was able to study the chromosomes of ascites tumors, "which turned out to constitute a very favourable cytological material."³⁹ There, during his first stay with Hauschka at Fox Chase, Levan began his research on mice. He left Lund for the United States in May 1951, returning before the end of the year.⁴⁰

37. Demerec to Levan, 18 Jan 1951, Levan to Demerec, 17 Apr 1951, Levan Papers.

38. On Svalöf, see Anna Tunlid, "Ärftlighetsforskningens gränser: Individer och institutioner i framväxten av svensk genetik" [Boundary of Genetics: Individuals and Institutions in the Development of Swedish genetics] (PhD dissertation, Lund University, Lund, Sweden 2004; includes an abstract in English). See also S. Ellerström and A. Hagberg, "The Cytogenetics Department of the Swedish Seed Association 1931–1961," *Sveriges Utsädesfören Tidskrift* 72 (1962): 192–209.

39. Levan to Demerec, 16 Nov 1951, Levan Papers, Folder Levan-Demerec Correspondence; Anderson, "Jack Schultz" (ref. 5), 405–6.

40. Levan to Tjio, 15 May 1951, Levan Papers, Folder Levan-Tjio Correspondence.

Theodore S. Hauschka came from Austria, graduated from Princeton University and obtained a PhD in zoology in the 1930s, after which he began research into cancer biology at the Institute of Cancer Research in Philadelphia, first at the Lankenau Hospital and later in the new institute setting at Fox Chase.⁴¹ Hauschka introduced Levan to research on inbred mice tumors and tissue transplantation, while Levan contributed to their collaboration with his skills as a cytologist, expert in obtaining slides and reproducing them for chromosome analysis. Levan brought to Philadelphia his expertise in the use of the camera lucida for drawing and classifying chromosomes.⁴²

After his first stay at Fox Chase, Levan brought the excitement of cancer research back to Lund.⁴³ Cancer research had been a public issue and a public policy issue in the United States since the late 1940s, due in large part to the growing political influence of the American Cancer Society and to the successful promoter and fundraiser Mary Lasker.⁴⁴ Levan's plant chromosome agenda was also in progress, and he was able to combine his interests. Since 1947, he had been collaborating with Indonesian agronomist Joe Hin Tjio. Tjio's research agenda had been forged during WWII and the postwar period. Born in Java, he had graduated from the Agronomy School in Bogor in 1942. During the Japanese invasion of Java during the war, Tjio was interned in a concentration camp in Bandung (Java). After his release, he left Java for Denmark in 1946, and with a fellowship from the Dutch government, continued his specialization in cytogenetics at the Royal Veterinary and Agricultural College in Copenhagen and, during the last half of 1948, at the laboratory of the Swedish Seed Association in Svalöf, Sweden, where he started his collaboration with Levan. In 1948, Tjio was appointed head of a cytology unit at the Agronomy Station Aula Dei in Zaragoza (Spain), where he worked on cereals and fruit cytogenetics. Each year from 1948 onward, Tjio spent leaves of

41. On the Institute of Cancer Research, see Robert F. Bud, "Strategy in American Cancer Research after World War II: A Case Study," *Social Studies of Science* 8 (1978): 425–59.

42. Michael Potter, "Brief Historical Sketch of Chromosomal Translocations and Tumours," *Journal of the National Cancer Institute Monographs* 39 (2008): 2–7. *The Buffalo News*, 1 Dec 1999, <http://www.princeton.edu/pr/news/99/c/1201.htm#Hauschka> (accessed 3 Dec 2014). See also Anderson, "Jack Schultz" (ref. 5), 405–6. On previous research by Hauschka, see Nikolai Krementsov, *The Cure: A Story of Cancer and Politics from the Annals of the Cold War* (Chicago: University of Chicago Press, 2002), 66.

43. Levan to Tjio 15 May 1951, Levan Papers, Folder Levan-Tjio Correspondence.

44. Stephen P. Strickland, *Politics, Science, and Dread Disease. A Short History of United States Medical Research Policy* (Cambridge, MA: Harvard University Press, 1972).

absence with Levan in Lund and Svalöf.⁴⁵ Funding for research on animal tumors, granted to Levan by the Swedish Cancer Society, allowed him to pay Tjio to spend increasing periods in Sweden from 1953 onward—between four and six months every year. During these periods, Tjio participated in Levan's shift in research focus to animal and tumor chromosomes, by collaborating with him in developing techniques for producing slides of clearly separated chromosomes and obtaining good photomicrographs of these slides.⁴⁶

In addition to his invitation to the Cold Spring Harbor Symposium, Demerec asked Levan to write on polyploidy for the volume *Advances in Genetics*, but Levan could not “fulfil [his] promises.” “My cancer work has taken all my time and is also much more interesting.” By then, a Swedish grant for a cancer laboratory at the Institute of Genetics in Lund had been secured, and Levan planned to return to the United States at the end of 1953.⁴⁷

Just as methods for rendering chromosomes visible circulated, mice strains with tumors were also circulating among researchers in Stockholm and Philadelphia. A mammalian adenocarcinoma, which had originated spontaneously in a female mouse at the Institute of Cancer Research in Philadelphia, was transformed into an ascites tumor by Georg Klein. Some animals infected in this way remained in Philadelphia and Buffalo, New York, Hauschka's later location. Others—the “ascites strain”—were brought to Stockholm. Georg Klein transported 200 mice himself by plane from Philadelphia to the Karolinska Institute in Stockholm, where he and Eva Klein developed the project they had envisaged together upon their arrival from Hungary in the late 1940s. It was after listening to Hans Lettré—who used ascites tumors in his biochemical studies—that Eva Klein suggested they culture tumor cells in the peritoneal cavity of the mouse, thereby avoiding tissue culture and obtaining the ascites directly from the animal.⁴⁸ The Kleins focused on the contents of

45. Santesmas, “Cereals, Chromosomes and Colchicines” (ref. 11).

46. Hauschka and Levan's tumour chromosomes research was funded by the National Cancer Institute of the National Institutes of Health and by the American Cancer Society, while Levan's work at that time was also funded by Swedish Cancer Society, enabling him to create a Cancer Laboratory at the Institute of Genetics in the University of Lund. Swedish funds for a cancer laboratory were agreed upon in early 1953. See Levan to Tjio, 29 Jan 1953, Levan Papers.

47. Levan to Tjio, 29 Jun 1953, Levan Papers, Folder Levan-Tjio Correspondence.

48. Albert Levan, “The Significance of Polyploidy for the Evolution of Mouse Tumours: Strains of the TA₃ Mammary Adenocarcinoma with Different Ploidy,” *Experimental Cell Research* 1 (1956): 613–29, on 615. On the Kleins, see Eva Klein and Georg Klein, “Nucleic Acid Content of Tumour Cells,” *Nature*, 166 (1950): 882; see also their own reconstruction in Klein and Klein, “How One Thing” (ref. 5), 11–13 and 15.

nucleic acids in cancer cells, at a time when nucleic acids were at the core of the research agenda for the Wallenberg Laboratory of the Karolinska Institute under the direction of Torbjörn Caspersson. The Kleins provided mice strains for Levan's experiments for quite a long time, and frequently witnessed his early presentations to Swedish colleagues on polyploidy in tumor cells. Tumor chromosomes circulated within mice and were "cultivated"—as Hanna Landecker has phrased it—in them, making the mice function as containers. Through this serial cultivation of tumours, mice bodies became both tool and object of chromosome research.⁴⁹ The experimental mice bodies recreated tumors, the chromosomes of which were produced and made visible.

"Would you be able and willing to work here on cancer chromosomes for some period during this fall?" Levan asked Tjio in April 1953. It was this circulation between Svalöf and Philadelphia that was creating space for chromosomes in cancer epistemology. A network developed: it was composed of Hauschka and Levan, based on a method invented by Eva and Georg Klein, and Tjio, who worked between Spain (Zaragoza) and Sweden (Svalöf and Lund), provided with the increasing funding available for cancer research. This medicalization of genetics contributed to the production of biomedicine, which was the medical mission of the biological laboratory under the aegis of postwar policies for medical research. Increasing funding would make cancer research appealing. Cancer research genealogy became a biological issue. Cytogenetic methods and tools contributed to the early medicalization of cytogenetics, which, in the 1960s, would lead to what would be called biomedicine and within it, medical genetics.⁵⁰

Through the handling of samples under the microscope and the camera lucida—the technical device Levan had at hand—material traces of the experiments were produced and placed in the chromosomes of tumor cells.⁵¹ These

49. Peyton Rous studied cancer tissue in chickens and propagated the sarcoma from generation to generation of chickens, by transplanting bits of the tumour from one chicken to another—the same method Eva and Georg Klein used to obtain ascites, propagating tumours and "cultivating them." On Rous, see Hanna Landecker, *Culturing Life: How Cells Became Technologies* (Cambridge, MA: Harvard University Press, 2007), 51. On the method to obtain ascites tumours from solid ones, see Klein and Klein, "Differential Survival of Solid Tumour" (ref. 30).

50. On biomedicine as a collection of superimposed biological disciplines acting upon medicine, see Jean-Paul Gaudillière, *Inventer la biomedicine: La France, l'Amérique et la production des savoirs du vivant (1945–1965)* (Paris: La Découverte, 2002).

51. See de Chadarevian, this Issue; also Maj A. Hultén, "Numbers, Bands and Recombination of Human Chromosomes: Historical Anecdotes from a Swedish Student," *Cytogenetic Genome Research* 96 (2002): 14–19.

experiments became a space for representing cancer cytogenetics by providing tumors with a biological meaning expressed in chromosome numbers and shapes, around the concept of polyploidy—of unusual numbers of chromosomes. Differences between normal cells and tumor cells, the old intriguing question, were to be found in their chromosomes.

The physical move of Levan himself from Lund to Philadelphia produced new links between plant cytogenetics and medical research in his collaborations with Hauschka. After “infecting” mice with ascites tumors introduced intraperitoneally, chromosomes were obtained by extraction following the animals’ deaths. The samples were then treated and chromosomes remade *in vitro*, the only way found to make them visible as proof of their existence, function, and malignancy.

Cancer Representations: Chromosome Images as Evidence

In March 1953, the U.S. Public Health Service approved the research grant submitted by Hauschka and Levan for their research on mouse cancer cells. In April, Levan presented early results of his work with Hauschka at a meeting of the Swedish Mendelian Society in Lund. On this occasion, cancer cytogenetics became visible to a broader audience, that of Swedish clinicians. The chromosome approach to cancer was novel, and the audience, among them “many medical people,” said Levan, “gave quite nice comments on the paper, showing that they appreciated the idea of this new approach to the cancer problem. . . . I was highly encouraged by the evident interest of the auditory [*sic*: audience] which was more numerous than I have ever seen before in the Mendelian Society,” he told Hauschka.⁵²

Hauschka was not surprised that the Mendelian society in Lund “turned up *in toto* to listen” to Levan: “The approach taken by us is beginning to be very fashionable and is the only way to get directly at the one and only theory of cancer origin which allows incorporation of all other theories, namely, the somatic mutation hypothesis.”⁵³ That is, cancer was regarded as being produced by mutations in somatic cells. Being a cytogeneticist, cancer could have appealed to Levan as a biological event with medical attributes.

52. Levan to Tjio, 16 Apr 1953, Levan Papers, Folder Levan-Tjio Correspondence.

53. Levan to Hauschka, 20 Apr 1953, and Hauschka to Levan, 4 May 1953, both in Levan Papers, Folder Levan-Hauschka Correspondence.

Genetic disorders were at this point included in their narratives on tumor polyploidy and reconstructed as a rationale for their research agenda. This was in tune with the promotion of cancer research in the mid-1950s and of the increasing funding for extramural programs of the U.S. National Cancer Institute.⁵⁴ There were also links with the stem cell hypothesis proposed by Theodor Boveri in his 1914 monograph—links which, by the early 1950s, included a cell mutation; according to this, cancer was characterized by the unlimited proliferation of a mutation in the cell that was expressed during cell division.⁵⁵

At the core of their explanation of tumor phenomena were the images Levan and Hauschka presented as evidence. Their findings were objects with particular shapes and numbers that characterized cancer tumors, forming biological cartographies of cancer. “The most important thing now,” said Levan to Tjio in April 1953, “is to work out the best possible techniques for analyzing tumor chromosomes. With that knowledge we will get a very strong position in the cancer chromosome research, which is taken up now by many laboratories all round the world.” Levan had confidence in Tjio’s skills in obtaining good slides: “only showing lantern slides of those beautiful chromosomes would justify a short paper.”⁵⁶ Levan was approaching the issue “as a cytogeneticist and not as an oncologist,” he told Hauschka, considered by Levan to be closer to oncology than he was himself. Levan was interested in discussing “the conditions governing the constancy of, and the occasional changes of the cancer cell population, as they are reflected by the chromosomal situation.” He said “it looks as if the tumor was *predestined* to give rise to a certain number of cell types,” thus suggesting a genetic origin of the tumor feature.⁵⁷ This

54. Ilana Löwy and Jean-Paul Gaudillière, “Disciplining Cancer: Mice and the Practice of Genetic Purity,” in *The Invisible Industrialist: Manufactures and the Production of Scientific Knowledge*, ed. J.-P. Gaudillière and I. Löwy (London: MacMillan, 1998), 209–49; Jean-Paul Gaudillière, “Circulating Mice and Viruses: The Jackson Memorial laboratory, the National Cancer Institute and the Genetics of Breast Cancer,” in *The Practices of Human Genetics*, ed. M. Fortun and E. Mendelsohn (Dordrecht: Kluwer 1999), 89–124.

55. See Creager, this Issue; also Boveri, *Zur Frage der Entstehung* (ref. 29); and Ulrich Wolf, “Theodor Boveri and his Book on the Problem of the Origins of Malignant Tumours,” in *Chromosomes and Cancer*, ed. J. German (New York: John Wiley), 3–20. See also Peo Koller, “Mitotic Anomalies in Tumours and Boveri’s Theory,” in his *The Role of Chromosomes in Cancer Biology* (Berlin: Springer Verlag, 1972), 14–21.

56. Levan to Tjio, 15 Apr 1953, Levan Papers, Folder Levan-Tjio Correspondence.

57. Levan to Hauschka, 15 Dec 1953, Levan Papers, Folder Levan-Hauschka Correspondence (emphasis added).

FIG. 5. Details of a figure showing an ink drawing of Landschütz tumor chromosomes. *Source:* Tjio and Levan, “Chromosome Analysis” (ref. 58), 32 (a, b). Reprinted with permission.

“predestination” was inscribed in the number of chromosomes, as revealed by the technique of obtaining them.

Rather than take a holiday over Christmas 1953, Levan carried out “nice hard work” on a joint paper with Tjio on one type of ascites tumor, the sarcomas I and II, which had originated spontaneously in the laboratory of Christoph Landschütz in Munich and been named the Landschütz tumors. They had carefully studied the “structural chromosome changes occurring,” and Levan took Tjio’s photomicrographs with him when travelling to Philadelphia in January 1954. In the meantime, Levan was awarded a prize by the Swedish Royal Physiographical Society for his work on “practical agriculture, especially for my production of tetraploids in sugar beets and clover,” recognizing fifteen years of practical breeding work and the usefulness of polyploidy in agriculture.⁵⁸ This was at the core of the contributions made by the Svalöf Experimental Station where Levan had trained, and the origins of Levan’s own agenda on animal tumors as cases of polyploidy. Tjio and Levan submitted their work on the Landschütz tumor to the proceedings of the Swedish Physiographic society—“a rather obscure journal, it’s true,” according to Levan—due to its excellent reproduction of pictorial material. Through the use of quinoline they were able to show small details of the chromosomes in the photomicrographs (Fig. 5).⁵⁹

Rather than fly from Sweden to New York, Levan went by ship: although this took longer, because of the amount of material he took with him—including his microscope—it was less expensive. Shortly after he left, research

58. Levan to Hauschka, 29 Dec 1953, Levan Papers, Folder Levan-Hauschka Correspondence. The images of the tumours are in Joe Hin Tjio and Albert Levan, “Chromosome Analysis of Three Hyperdiploid Ascites Tumours of the Mouse,” *Lunds Universitets Årsskrift. N. F. Avd. 2. Bd* 50, no. 15 (1954): 1–39.

59. Levan to Hauschka, 11 Jan 1954, Levan Papers, Folder Levan-Hauschka Correspondence.

carried out by Eva Melander with mice in Lund led Levan to postulate the hypothesis of a cancer “infection”: “for the first period after transplantation the cancer cells are perfectly alike any somatic cell. . . . Gradually, however, as they propagate they take on their normal malignant appearance.” Levan reflected on this fact by pointing out that for Eva Melander and himself, “as cytologists it was quite a thrill to be able to recognize one cell as a normal body cell with 40 chromosomes and other cells, looking just the same, as potential cancer cells with 46 chromosomes” Levan reasoned that these cells became cancerous because of the higher chromosome numbers.⁶⁰

Hauschka was planning his move from Philadelphia to a new post at the Roswell Park Memorial Institute in Buffalo, New York. He asked Levan to come with him to Buffalo, but Levan, although pleased, did not accept.⁶¹ In the middle of the move, Hauschka informed Levan that the *Journal of the National Cancer Institute*, in which they planned to publish one of their collaborative papers, was no longer interested in illustrations. Images were considered a “printing luxury” by the *Journal* if used to show “points already established”. For Levan, images were the most important evidence, and as Hauschka knew Levan well, he asked Levan “not to be alarmed by this.” However, in the end, their paper appeared without images.⁶² Shapes and numbers were evidence in the form of images—drawings and photomicrographs. In their 1958 paper they employed descriptions in words only. They encoded the art of describing by translating images into text; evidence was produced out of a textual, literary narrative instead of from a visual narrative.⁶³ The medicalization of cytogenetic practices was displacing drawings to the margins as technologies providing experimental evidence.

In his own contributions to the subject, Levan kept chromosome images at the core of his reasoning and his explanations of tumor developments, shapes, and numbers.⁶⁴ Slides carried Levan’s cytological conception of cancer cells

60. Levan to Hauschka, 11 Jan 1954, *ibid.*

61. Levan to Hauschka, 13 Sep 1954, *ibid.*

62. Theodore Hauschka and Albert Levan, “Cytologic and Functional Characterisation of Single-Cell Clones Isolated from the Krebs-2 and Ehrlich Ascites Tumors,” *Journal of the National Cancer Institute* 21 (1958): 77–111.

63. Svetlana Alpers, *The Art of Describing: Dutch Art in the Seventeenth Century* (Chicago: University of Chicago Press, 1983); Spanish version (Madrid: Blume, 1987), 19.

64. Hauschka to Levan, 5 Oct 1954, Levan Papers, Folder Levan-Hauschka Correspondence. For the published paper, see Hauschka and Levan, “Cytologic and Functional Characterisation” (ref. 62). Levan published some others on his own in which he included many plates, photomicrographics, and “Indian ink drawings,” as he called them, in articles published in 1956 in

and were at the core of his scholarship. He and Tjio contributed to the technology that moved chromosomes from within the tumor cell to the flat bidimensional image on a slide. Cytogenetics' visual epistemology revealed the cognitive work of chromosome images: they operated at the interface between cytogenetics and pathology, a morphological alphabet composed of biological forms and meanings.⁶⁵

In March 1955, Levan presented a "good summary" of the results of his work in Philadelphia and Lund to an audience of clinicians, microbiologists, and geneticists at a meeting in Uppsala. Among those in attendance were Eva and Georg Klein from Stockholm. Later, in May, two full-day conferences on "Ascites Tumours as Tools in Quantitative Oncology," organised by Hauschka, were held at the New York Academy of Sciences. Levan's presentation—"I intend to read a paper of about the same character as in Uppsala"—was a review of tumor cytology, and included Levan's drawings and chromosome images.⁶⁶ Hauschka encouraged Levan to include visual evidence: "I hope that the main emphasis in your ascites conference talk will be on evidence of quantitative intra-chromosomal rearrangements." Levan's contribution to the ascites conference in New York became a further opportunity to present his visual epistemology of chromosome images, as can be read in the abstract he submitted on ideograms, chromosome structures, and sizes under the general title of "Chromosomes in Cancer Tissue." Levan discussed chromosome differences between tumors and "their original host species." He took the issue of "numerical conditions," presented in beautifully clear photomicrographs taken with Tjio, and mentioned the near-tetraploid mouse carcinomas, Ehrlich and Krebs 2 ascites tumors.⁶⁷

Cancer and in *Experimental Cell Biology*, and with Tjio in *Anales de la Estación Experimental Aula Dei* and in *Hereditas*.

65. See Barbara M. Stafford and Frances Terpak, *Devices of Wonder: From the World in a Box to Images on a Ccreen* (Los Angeles, CA: Getty Research Institute, 2001); and Barbara M. Stafford, *Echo Objects: The Cognitive Work of Images* (Chicago: University of Chicago Press, 2007). For a study on chromosome images both as knowledge and as artisan practice, see María Jesús Santesmases, "Sample, Cultures and Plates: Early Human Chromosomes", in *Microscope slides. Reassessing a neglected historical resource*, ed. Ilana Löwy (Berlin: Max Planck-Institut für Wissenschaftsgeschichte, 2011), 25–34.

66. Tjio to Levan, 10 Mar 1955, Levan Papers, Folder Levan-Tjio Correspondence.

67. "Your beautiful abstract has been slightly edited by me," said Hauschka to Levan, 27 Apr 1955; see also Hauschka to Levan, 22 Mar 1955; both in Levan Papers, Folder Levan-Hauschka Correspondence. Albert Levan, "Chromosomes in Cancer Tissue," *Annals of the New York Academy of the Sciences* 63 (1956): 774–93.

HUMAN CHROMOSOMES FROM TISSUE TRANSPLANTATION

Early in 1955, Levan began research into human tumors. He was already working on human tumor “fixation” by March 1955; that is, he was trying to obtain good chromosomes from human tumor cells in cooperation with medical institutions at the University of Lund.⁶⁸ However, he needed Tjio and his skill at creating good photomicrographs: “I know I cannot make them by far as perfect as you do.” As Levan faced experimental difficulties when handling these human tumor cells, he planned to visit Chinese-American cell biologist Tao-Chiuh Hsu and tissue culture expert Charles Pomerat at the University of Texas in Austin to “learn how they make their tissue culture chromosomes” extracted from human bodies.⁶⁹ He asked Hauschka for advice regarding this contact, and Hauschka responded by offering Levan a human cell strain called HeLa, which “one of our people has grown *in vitro* here.” Instead of travelling to Texas, Levan could now visit Hauschka at Roswell Park.⁷⁰ HeLa cells, named after the woman from whom the tumors were extracted—Henrietta Lacks—would become tools within biological research for decades to come, and are still in use.⁷¹

After participating in the conference on ascites tumors organized by Hauschka, Levan went to Buffalo to work with him, and subsequently spent a month in New York working on “human tumour implants.” He had written to Helene W. Toolan at the Sloan-Kettering Institute for Cancer Research (New York), with the intention of spending some time visiting her. Toolan had invented a method for introducing human tumor cells into mice by treating the mice with cortisone prior to the introduction. Her technique “of carrying human tumours in animals” was useful for overcoming “the difficulty of obtaining fresh samples of one and the same tumour at any time” for chromosome studies.⁷² Toolan, however, was on leave that year, but Levan

68. Levan, “Chromosomes in Cancer Tissue” (ref. 67), 775.

69. Levan to Hauschka, 10 Mar 1955, Levan Papers, Folder Levan-Hauschka Correspondence. On Hsu and Pomerat, see S. Pathak, “T. C. Hsu: In Memory of a Rare Scientist,” *Cytogenetics and Genome Research* 105 (2004): 1–3.

70. Hauschka to Levan, 22 Mar 1955, Levan Papers, Folder Levan-Hauschka Correspondence.

71. See Landecker, *Culturing Life* (ref. 49); Rebecca Skloot, *The Immortal Life of Henrietta Lacks* (New York: Broadway Paperbacks, 2010).

72. Albert Levan, “Chromosomes Studies on Some Human Tumors and Tissues of Normal Origin, Grown in Vivo and in Vitro at the Sloan-Kettering Institute,” *Cancer* 9 (1956): 648–63, on 648.

was invited by the director of Sloan-Kettering, C. P. Rhoads, to work with the group under the supervision of cytologists John Beisele and Alice Moore.⁷³

Toolan's research on the conditions required for transplanting human tumors into laboratory mice led her to implant them—immediately after removal from the patient—in Albino rats from the Wistar Institute and hamsters from the Lakeview Colony. She provided both a method for transplantation and a complete study of many tumors. Her aim had been to design a method enabling any mouse to accept a tumor, to facilitate the testing of prospective cancer therapeutic agents, one of the main approaches under study at Sloan-Kettering for the control of cancer.⁷⁴ Both X-radiation and cortisone injection made transplants durable; tumors did not survive in nontreated animals. By creating living conditions for a tumor, mice bodies themselves became laboratories. Toolan used young, weanling rats that would grow as the tumor within them grew.⁷⁵ This growth allowed the testing of chemotherapeutic agents against cancer and contributed to the fame of Sloan-Kettering as “one of the best cancer research centres in the world,” as a British physician phrased it when praising the director, Cornelius P. Rhoads.⁷⁶ human cancer in experimental mice bodies, Levan obtained excellent slides of human chromosomes, both from tumor cells and “from tissues of normal origins.” “Your implants are ideal for chromosome studies and easy to handle,” he told Toolan.⁷⁷ His results were included in a paper sent in December 1955 to *Cancer*, the journal of the American Cancer Society, and published in July 1956 (Fig. 6).⁷⁸

On his return to Lund, and with new experimental skills in handling human implants, Levan collaborated with Tjio, who spent April and August of 1955 on leave from the experimental station Aula Dei in Zaragoza. For their

73. Levan to Hauschka, 28 Mar 1955, Levan Papers, Folder Levan-Hauschka Correspondence. On Bieselee, see William Powers Jr. and Sue Alexander Greninger, “In Memoriam: John Julius Beisele,” <http://www.utexas.edu/faculty/council/2009-2010/memorials/bieselee.html> (accessed 3 Dec 2014). On Rhoads and the Sloan-Kettering Institute during this period, see Bud, “Strategy in American Cancer Research” (ref. 41).

74. Bud, “Strategy in American Cancer Research” (ref. 41).

75. Helene W. Toolan, “Conditioning of the Host,” *Journal of the National Cancer Institute* 14 (1953): 745–65; Helene W. Toolan, “Growth of Human Tumours in Cortisone-Treated Laboratory Animals: The Possibility of Obtaining Permanently Transplantable Human Tumours,” *Cancer Research*, 13 (1953): 389–94 plus 15 plates unpagged; Toolan, “Transplantable Human Neoplasms” (ref. 9).

76. G. Hadfield, “Dr. C. P. Rhoads, M.D.,” *Annals of the Royal College of Surgeons England* 25, no. 4 (1959): 264–67.

77. Levan to Toolan, 21 Sep 1966, Levan Papers, Folder Levan-Toolan Correspondence.

78. Albert Levan “Chromosomes Studies on Some Human Tumors” (ref. 72).

FIG. 6. A chromosome number "of around the tetraploid": chromosomes of a human epidermoid carcinoma. Source: Levan, "Chromosomes Studies" (ref. 72), 652. Reprinted with permission.

collaboration in the study of chromosomes from tissue culture, they were allowed to use a small tissue culture laboratory at the Institute of Bacteriology of the University of Lund. "We had the nice experience of obtaining slides of human chromosomes of a quality which I don't think has been seen before, in all of which we counted forty-six instead of the expected forty-eight in four different embryo lung fibroblasts."⁷⁹ To obtain a good slide, the embryo tissue sample was treated according to the method described by Hsu in 1952 and used by Levan in his paper on cancer chromosomes.⁸⁰ Levan and Tjio obtained their well-known slide of forty-six human chromosomes through colchicine and hypotonic treatment, and the slide and ideogram were published in May 1956, in the Swedish journal of the Mendelian Society of Lund, *Hereditas*. The paper by Levan on human tumor transplants in mice, although submitted earlier, was published in *Cancer* that August. This order of events has since been the subject of long and bitter controversies over whether the new number was Tjio's achievement, or Levan's, or even a combination of the skills of both of them.⁸¹ This new number has its roots in cytology at the very origins of

79. Levan to Hauschka, 2 Mar 1956, Levan Papers, Folder Levan-Hauschka Correspondence.

80. Levan, "Chromosome Studies" (ref. 72).

81. De Chadarevian, this Issue; Ulfur Arnasson, "50 Years After—Examination of the Circumstances around the Establishment of the Correct Chromosome Number of Man," *Hereditas* 143 (2006): 202–11; Hultén, "Numbers, Bands and Recombination" (ref. 51); Albert Levan, "The Background to the Determination of the Human Chromosome Number," *American Journal of Obstetrics and Gynecology* 130 (1978): 725–26; Joe Hin Tjio, "The Chromosome Number of Man," *American Journal of Obstetrics and Gynecology* 130 (1978): 723–24.

cytogenetics and in close collaboration, as Levan liked to argue, with medical institutions dedicated to cancer research—as were both the Institute for Cancer Research in Philadelphia and Sloan-Kettering. Hsu was influential with a paper in which he confirmed the old number forty-eight for human somatic chromosomes.⁸² Hsu's data fit the old recognized and accepted number of forty-eight, but it was Hsu's experimental skills as a cytologist that were influential on Levan. In collaboration with Tjio, Levan followed Hsu's technique of culturing embryo tissues to obtain clear, beautifully drawn chromosomes, which Levan consistently achieved with his camera lucida. In 1952, Hsu had obtained clear photomicrographs, but his camera lucida drawings did not have the clarity of those included in Tjio and Levan's 1956 paper, and were not as clear as Levan's earlier drawings from his papers on *Allium cepa* chromosomes treated with colchicine during the 1930s. Levan was in search of even better images that would fit into his own trajectory as a master of cytological drawing; he was in search of accessible ways to study chromosomes and “would like to improve a little” the chromosome pictures of Hsu and Pomerat.⁸³

CONCLUSIONS: CANCER AS AN ORIGIN OF MEDICAL GENETICS

So far in this essay I have shown the pathway toward Levan and Tjio's slides of normal, healthy human cells as originated from research into the chromosome morphology of cancer cells. The early atomic age provided increasing funding and public support for cancer research, not only in the United States but also in Sweden, the Swedish Cancer Society funding some of Levan's travels to the United States and his research project on cancer chromosomes at the Institute of Genetics in Lund. A circulation of practices was at the core of this set of events, the exploration of which contributes to our understanding of the origins of medical genetics, and of the revised number of human chromosomes: forty-six instead of the forty-eight widely accepted among cytologists and geneticists.

82. T. C. Hsu, “Human Chromosome in Vitro: The Karyotype of Man,” *Journal of Heredity* 43 (1952): 167–72; T. C. Hsu and Charles M. Pomerat, “Mammalian Chromosomes in Vitro. II. A Method for Spreading the Chromosomes of Cells in Tissue Culture,” *Journal of Heredity* 44 (1953): 23–29; both cited by Levan, “Chromosome Studies” (ref. 72).

83. See Levan to Hauschka, 2 Jul 1955, Levan Papers, Folder Levan-Hauschka Correspondence. The paper that inspired them, in addition to those cited in the previous note, was surely Hsu and Pomerat, “Mammalian Chromosomes in Vitro” (ref. 82).

Cytogenetics, as a practice of cell biology, developed into tumor representation in plants and mice in the 1950s, in research being done in Sweden, the United States, and Spain. By emphasizing geographical and interdisciplinary circulation, I aim to show that the construction of knowledge and practices in genetics resulted from the travels and exchanges at the origin of medical genetics—regarded as a clinical discipline that emerged immediately after publication of the new number of human chromosomes provided by Tjio and Levan in 1956.⁸⁴ By “making chromosomes”—to use the words they used—biology recreated itself from tiny bases: that of the shapes and sizes of chromosomes able to correlate with cancer. Researchers, research objects, and research tools circulated, moving with the physical journeys of people, microscopes, slides, and experimental skills. This was a dynamic space under construction: the sharing of materials, instruments, and methods created the experimental culture of cytogenetics, moving toward human cytogenetics, from plants through mice.

The experimental trajectory from tumor cells produced by the action of colchicine was followed in Levan’s agenda by his interest in animal tumors. He was first introduced to the study of fluid tumors extracted from mice by Hauschka in Philadelphia, and then, when doing research on the cell biology of cancer, he moved to human cells. Requirements for handling different experimental materials led Levan to Philadelphia; already an expert in plants, here he obtained good chromosome slides and produced ideograms, chromosome drawings by camera lucida projections as a system of signs. In the meantime, he began his collaborations with Indonesian agronomist Joe Hin Tjio, a researcher at the Botanical Garden in Bogor (Java). Tjio, with his skills as an agronomy engineer and plant cytologist, belonged to the postwar period; coming from a concentration camp in Java during the Japanese invasion in World War II of the Dutch colony, he then moved to Copenhagen, and later to Zaragoza. An exceptional slide producer and photomicrographer, as Soraya de Chadarevian demonstrates, from 1948 onward he combined his breeding work at Aula Dei agricultural experimental station in Zaragoza (Spain) with his permanent collaboration with Levan.⁸⁵ Cooperation made them travel—Tjio from Zaragoza to Lund and back at least once a year, and Levan from Lund to Philadelphia and back, also once a year—from 1952 on, including a 1955 trip to New York. While maintaining their agendas as plant breeders—for which

84. Lindee, *Moments of Truth* (ref. 11).

85. De Chadarevian, this Issue.

Levan was fully recognized in Lund and Tjio in Zaragoza—cancer as a research subject migrated from plants to mice and then to human tissue. Techniques, objects, and people moved from Europe to the United States and back, cancer and cytology becoming challenges that developed as a project on cancer cell morphology.

Chromosomes, as the cellular sites of hereditary transmission and of polyploidy, received and sheltered many skills and research agendas at that particular moment of the atomic era. Cancer and cell growth were research objects, and the size and shape of tumor cell chromosomes—much larger than usual cells and endowed with particular growth pathways—were biologically intriguing. Alongside this were Tjio's skills in chromosome slide preparation, and the compelling biological mysteries of cancer and cell malignancy development in the early Cold War atomic age, when the promotion of research into radiation included projects on animal and human genetics.

Mutation as a cancerous phenomenon linked the Cold War science policy of increasing support for radiation research and radiation genetics, with the transformation of a dread disease into "a biomedical venture," as Jean-Paul Gaudillière has phrased it.⁸⁶ Biology and the postwar increase of funds for cancer research mutually interacted to develop a corpus of knowledge in which chromosome research was promoted and mutation phenomena were investigated as a cause of cancer tumors. As polyploidy was a mutation phenomenon, according to the theory of Hugo de Vries and the practices of cytology dating back at least to the work on *Oenothera* carried out by Anne May Lutz, polyploidy provided an explanation for cancer as a genetic event: it was at the chromosome level that mutation, and thus polyploidy, took place. Chromosomes and the phenomena in which they participated during cell division were the materiality of what was then understood as genetics—and heredity: they operated as agents in a biological pathology. Tumors were found to have tetraploid chromosome numbers, multiples of the diploid somatic number; chromosomes were found to multiply during mitosis. By reading the unusually high chromosome numbers in tumor cells in mice as polyploidy, Levan and Hauschka condensed their individual expertise into a shared perspective of cancer tumors from a biological point of view. Pathology and cytogenetics hybridized and provided images as explanations for the behaviour, size, and growth of tumor cells. Research on cancer chromosomes resulted from this particular combination of skills and environment.

86. Gaudillière put it this way regarding Western medicine, see his "Cancer" (ref. 10).

The power of radiation politics, if it can be phrased as such, not only provided funding and the promotion of particular tools but also provided ways of thinking and practicing biological experiments, of establishing connections between biology and medical practices through chromosomes as part of the development of contemporary biomedicine.⁸⁷ In this set of objects and practices, cytogenetics was medicalized. Medicine's ontological superiority, compared to biology, enabled this asymmetrical interaction that transformed medical practice—in this case in relation to cancer—from that time forward.

Created and recreated in mice bodies as reactive containers, cancer was incorporated into living bodies that behaved as living reactors.⁸⁸ These living test tubes condensed, in their bodies, the wide laboratory that life in all its forms has become since the first atomic bombs were dropped on Hiroshima and Nagasaki in 1945. As developed in mice bodies by Eva and Georg Klein, ascites tumor culturing was a life-technology, following Lily Kay, for the genetic agenda of cancer at the Institute of Cancer Research in Philadelphia, where Hauschka and Levan performed their collaborative experiments.⁸⁹

According to Anna Tunlid, Levan personified the success of connections between disciplines in the construction of genetics in Sweden as a disciplinary space wider than botany or agronomy—or, as I suggest, by integrating them into his own biomedical trajectory.⁹⁰ Hauschka, Eva and Georg Klein, Helene Toolan, Levan, and Tjio participated in a story that included the breeding of mice, the development of techniques, their mutual training, and the exchanging of research materials and problems. These practices as a process of doing experiments were represented by the ideogram of large and numerous chromosomes, drawn and redrawn to provide evidence of both the regularities and the irregularities that characterized tumor cells. The skills of those involved literally crossed geographical and disciplinary boundaries, by way of policies for cancer research, as part of an intellectual history of contemporary medical

87. On the meaning of biomedicine and in addition to Gaudillière, *Inventer la biomedicine* (ref. 50), and Löwy, *Between Bench and Bedside* (ref. 32), see Joan H. Fujimura, *Crafting Science: A Sociohistory of the Quest for the Genetics of Cancer* (Cambridge, MA: Harvard University Press, 1996).

88. On the standardized inbred *Drosophila* “breeder reactor,” see Robert E. Kohler, *Lords of the Fly: Drosophila Genetics and the Experimental Life* (Chicago: University of Chicago Press, 1994), 49.

89. Lily E. Kay, “Life as Technology: Representing, Intervening and Molecularizing,” in *The Biology and History of Molecular Biology: New Perspectives*, ed. Sahotra Sarkar (Dordrecht: Kluwer 1996), 87–100.

90. Tunlid, “Ärfilighetsforskningens gränser” (ref. 38).

research that suggests cancer and tumor cell chromosomes as an origin of a biomedical space; that of the knowledge and practices of medical genetics.

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