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Ludwik Gross, Sarah Stewart, and the 1950s discoveries of Gross murine leukemia virus and polyoma virus

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ABSTRACT

The Polish-American scientist Ludwik Gross made two important discoveries in the early 1950s. He showed that two viruses— murine leukemia virus and parotid tumor virus— could cause cancer when they were injected into susceptible animals. At first, Gross's discoveries were greeted with skepticism: it seemed implausible that viruses could cause a disease as complex as cancer. Inspired by Gross's initial experiments, similar results were obtained by Sarah Stewart and Bernice Eddy who later renamed the parotid tumor virus SE polyoma virus after finding it could cause many different types of tumors in mice, hamsters, and rats. Eventually the "SE" was dropped and virologists adopted the name "polyoma virus." After Gross's work was published, additional viruses capable of causing solid tumors or blood-borne tumors in mice were described by Arnold Graffi, Charlotte Friend, John Moloney and others. By 1961, sufficient data had been accumulated for Gross to confidently publish an extensive monograph—*Oncogenic Viruses*—the first history of tumor virology, which became a standard reference work and marked the emergence of tumor virology as a distinct, legitimate field of study.

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1. Introduction

From the mid-1960s to the end of the 20th century, tumor viruses were the primary vehicles for studies of cancer at the molecular level. In the era before gene cloning, tumor viruses provided a system with a small number of genes that could be manipulated to investigate the genetic basis of cancer. The first oncogenes were discovered using tumor viruses. Historians of biology rightly focus on the characterization of oncogenes and the elucidation of their modes of action as high points in the molecular biology of the 1970s and 1980s (see, for example, Morange, 1998, chap. 19). Less discussed but no less important, are the earlier developments in 1950s virology that were necessary for tumor viruses to become widely used tools to investigate cancer. The pivotal 1950s discoveries of viruses that are oncogenic in mice and the invention of robust experimental procedures, by Ludwik Gross in particular, to increase the chances of such discoveries made have not received sustained study by historians of biology. His work on murine oncogenic viruses can be seen as a bridge between the early work of Peyton Rous on chicken viruses and Richard Shope on rabbit viruses, and the post-1960s focus on tumor viruses and cultured cell lines. This paper will follow the early to mid career of Ludwik Gross and detail how two different oncogenic mouse viruses were discovered: a leukemia virus and a tumor virus, one causing a blood disorder and the other solid tumors. The successes of the 1950s, and advances in cell culture and quantitative assays of viral transformation, allowed 1960s and 1970s tumor virology to flourish and eventually provide deep insights into the genes implicated in many mouse and human cancers. Gross's career also illustrates a high point in what I call the golden age of the cancer virus hunter. Then it was possible—perhaps for the last time—for solitary researchers to stand on the cutting edge of research and discover important new tumor viruses. The narrative ends with a description of the genesis of the first monograph on tumor virology, *Oncogenic Viruses* written by Gross. This 1960 publication marked the coming of age of the new field of tumor virology and provided a strong biological foundation on which future molecular studies of tumor viruses could confidently stand.

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2. The beginnings of Ludwik Gross's career

It was September 1939 and the beginning of WWII. German troops were invading Poland and the Polish army was in retreat. Dr. Ludwik Gross was driving a friend's abandoned car, desperately trying to make it to the Romanian border before the German army caught up with him. He had moved his mother and sister from their home in Krakow to Lwów[1] to avoid any bombing of Krakow and now was making a run for the Romanian border. He had a serious setback: the car had run out of gasoline.[2] Would he make it to freedom?

Ludwik Gross (1904–1999) was born into a prominent Jewish family. His father Adolf Gross (1862–1936) was a lawyer who represented the Jewish population of Krakow in the Austro-Hungarian parliament. Adolf was known for passing a bill to support widows and orphans of WWI. Ludwik entered medical school at Jagiellonian University in Krakow in 1923 and graduated in 1929. While in residency at St Lazar General Hospital in 1931 and 1932, he operated and assisted on cancer of the lip, which often occurred in peasants who smoked pipe tobacco. He noticed that the disease often had spread to the lymph nodes and moved in what appeared to be a manner similar to infections.[3] Gross was a medical columnist and wrote science articles for a widely read Krakow newspaper *Ilustrowany Kuryer Codzienny* (Illustrated Daily Courier).[4] The wife of the newspaper publisher became sick during a visit to Paris and asked for Gross to come to Paris to consult with her French physician. Gross took a train to Paris and as well as looking after Mrs. Marion Dabrowska, visited the Pasteur Institute. He discussed with the immunologist Alexandre Besredka (1870–1940) the idea that tumors may be caused by transmissible viruses. Besredka was interested enough to invite Gross to the Pasteur Institute as a temporary guest investigator. He would work at the Pasteur Institute for eight years.

3. Early tumor research in Europe

Gross brought to Paris a mouse tumor called Sarcoma 37. This well-studied transplantable sarcoma was discovered in 1907 at the Imperial Cancer Research Fund in England (Craigie, 1952). Following his mentor's interests, Gross spent years trying to immunize mice against transplanted tumors. His work at the Pasteur Institute steeped him in its traditions and rigors of research. He also could feed his fascination about the nature of scientific discovery by speaking with a number of the eminent scientists from the previous generation.[5] Gross and Besredka obtained some positive results good enough to be presented at the Académie des Sciences in 1935: tumor cells implanted below the skin of mice are fatal but tumor cells implanted intradermally sometimes immunize mice against future implants from that tumor. However, despite years of effort, Gross and Besredka could not identify a virus that caused cancer.

To publicize his results, Gross wrote to Peyton Rous (1879–1970), the father of American tumor virology, at the Rockefeller Institute.[6] A year later Gross wrote again, this time looking for a job at the Rockefeller Institute. Rous thought that Gross had a tendency to make excessive claims based on relatively little evidence. He also thought that Gross's reputation would be enhanced if he published less with Besredka and more by himself.[7] For his part, Besredka held Gross in high regard writing that he was driven by a "feu sacré" (sacred fire) and that he thought of him as he would a son.[8] Not surprisingly given the competition from numerous American researchers also looking for a position, Gross was not offered a job at Rockefeller Institute.

In the fall of 1938, Gross traveled to the US on the French Line steamship *S.S. Paris* to look in person for a position. He met with the Surgeon General Thomas Parran. He inquired at Yale, Columbia, Memorial Hospital, the Cleveland Clinic, and the Rockefeller Institute, but once again came up empty handed. As he put it, "nobody [I spoke with] believed at the time in the existence of a cancer or leukemia virus."[9] As Creager and Gaudillière (2001) point out, in the 1920s and 1930s the most popular theories of cancer causation focused on the role of chemicals.

Reluctantly Gross returned to Europe to consider an offer of a position at the Maria Sklodowska-Curie Radium Institute in Warsaw. Within a couple of months and before Gross could begin work in Warsaw, the Germans attacked Poland. Gross decided to flee to Romania, which had opened its border to Polish refugees. Among other things the Germans would shut down his newspaper. Luckily for Gross and the future of tumor virology, he was able to beat the invading German army to the Romanian border. It is unclear whether he managed to find gasoline for the car or abandoned it before the border, but either way his escape was successful. While staying in Bucharest, Gross planned to return to the United States. To raise the necessary funds, Gross sold his Citroen that he had stored in Paris and bought a ticket on the *S.S. Rex* from Genova to the United States. He now needed to get to Italy and obtain a visa to enter the United States. Using his publishing contacts—the New York Times correspondent in Bucharest—Gross met with the United States Ambassador, who gave him a visitor's visa. He also wrote to Pietro Rondoni, the Director of the National Cancer Institute in Milan to obtain an official invitation to visit so that he, as an Eastern European Jew, could obtain an Italian Visa. Gross traveled to Paris to close his laboratory and then to Italy to board the *SS Rex*. While he was crossing the Atlantic, France fell to the German army.

4. A new start in the United States

Although there was no Poland to which to return, Gross was still allowed to enter the US on his visitor's visa. He traveled to Cincinnati to take a position at a Jewish Hospital. Gross passed the New York State licensing board exam in medicine—New York State allowed people to take the exam before they had full US citizenship—and then applied for a commission in the United States Army Medical Corps. Being grateful for being let into the country, joining the Army was one way for Gross to pay back the United States.[10] He

[1] Document labeled "Miss M Culter 1941?" Ludwik Gross Papers, MSC 504, Personal and Biographical, National Library of Medicine, Bethesda, Maryland, hereafter Gross Papers.

[2] Augusta Gross Interview, New York, November 1, 2013.

[3] Unpublished MS "The Search for Viruses as Etiological Agents in Cancer and Leukemia" p. 2. Gross Papers. The manuscript appears to an expanded version of Gross (1976). Augusta Gross also holds a copy of this manuscript. Also see Bessis (1976).

[4] Gross ended up publishing two books popularizing science in Polish: Gross (1946, 1951a).

[5] Augusta Gross, personal communication Feb 16, 2014. Letter, Gross to Bittner, April 23, 1944, Gross Papers. Gross spoke with Amédée Borell (1867–1936), Charles Nicolle (1866–1936), Emile Roux (1853–1933), Albert Calmette (1863–1933), Charles Oberling (1895–1960), and Jules Bordet (1870–1961) about their work and also to get some "tips" on the communicability of cancer. Some of his interviews were published in the Polish newspaper.

[6] Letter, Gross to Rous, September 3, 1935, Peyton Rous Papers, American Philosophical Society, Philadelphia, PA, hereafter Rous Papers. See Van Helvoort (1994), Becsei-Kilborn (2003, 2010) and Sankaran (2014) for more on the career of Peyton Rous and Rous (1910, 1911) for some of the original work.

[7] Letter Rous to Gasser, Sept 25, 1936, Rous Papers.

[8] Translation of a letter dated November 30, 1936. Gross Papers.

[9] Unpublished MS, p. 6.

[10] Augusta Gross interview.