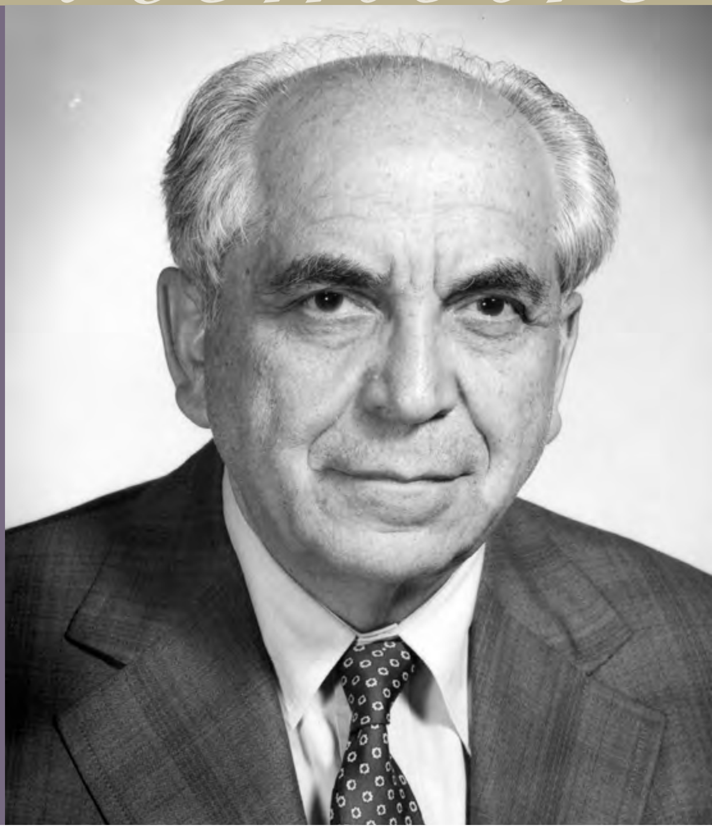
Ludwik Gross

1904–1999

BIOGRAPHICAL *Memoirs*



A Biographical Memoir by
Robert C. Gallo

NATIONAL ACADEMY OF SCIENCES

LUDWIK **GROSS**

September 11, 1904–July 19, 1999

Elected to the NAS, 1972

Ludwik Gross, elected to the National Academy of Sciences in 1972, was one of the great pioneers of cancer research, and the father of modern retrovirology. Although he discovered the first two mammalian cancer viruses and was the first to demonstrate that leukemia in mammals was transmitted by a virus, there was a painfully long period of time before he gained proper recognition from his peers, and even today he is not recognized to a degree nearly commensurate with his achievements. Ludwik managed to achieve great discoveries despite a lack of adequate funding and against a strong headwind of general belief that leukemia and other cancers could not possibly be caused by viruses, a general belief that bordered on hostility.

By Robert C. Gallo

Early life

Ludwik Gross was born in Cracow, Poland, in 1904. He took an interest in medicine from an early age. He attended and obtained his medical degree at Jagiellonian University in Cracow in 1929. Following this, he trained in internal medicine at St. Lazar General Hospital, also in Cracow, in the early 1930s. His focus at this time was on cancer of the lip, and he was particularly impressed by the frequency with which the cancer metastasized to lymph nodes, which he thought was brought about by a mechanism similar to infectious processes.

By the 1930s he was at the Pasteur Institute, where he worked with Alexandre Besredka on the origins and immunologic aspects of cancer. One of his main areas of research was attempting to immunize mice against transplantable tumors, with some success but generally inconsistent results. He also wrote medical articles for newspapers in Poland during this time.

Ludwik attempted to secure a research position in the United States, but was unsuccessful. In 1939 he was offered a position at the Marie Curie Radium Institute in

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Warsaw, and left to explore that option. While he was visiting Poland, the Nazis invaded, and he was able to very narrowly escape to Romania in a borrowed car. From there by way of France and Italy, he emigrated to the United States. While he was en route, France fell to the Nazis. This was his second rather narrow escape.

Arrival in the U.S.

After arriving in the United States, Ludwik continued to study tumor immunology at Christ Hospital in Cincinnati. He was also interested in retinoblastoma, and wondered whether the familial pattern of incidence was indicative of vertical transmission of a virus (retinoblastoma, it turns out, is genetically transmitted). He enlisted as a captain in the U.S. Army Medical Corps, where he served during World War II. It was at this time that he also married his wife, Dorothy.

By the end of the war Ludwik had been assigned to the Veteran's Hospital in the Bronx. He was able to continue his research by working after hours. After leaving the service, he remained at the Bronx V. A. Hospital, where he became the head of cancer research. There he spent the bulk of his career and made all of his important discoveries.

It is hard to imagine what the research environment was like back then: funding was very difficult to obtain; there was not the support from industry or government that we have today. The large research infrastructure that scientists take for granted today was yet to be developed.

Techniques were quite crude by modern standards, and consequently they were not very powerful. There was not a variety of carefully designed and pretested kits for every imaginable procedure, and researchers generally made all their own reagents, including buffers, and even purified their own enzymes and synthesized their own substrates. Given these conditions, Ludwik's accomplishments are all the more impressive.

On the other hand, during that time, there was not the huge array of regulations that we operate under today. Ludwik's early line of experiments on the transmissibility of murine leukemia required that he maintain a breeding colony of inbred mice. The inbred strain that he focused on was the AKR strain (a mouse strain developed by Jacob Furth), because they had a relatively high incidence of spontaneous leukemia. Due to a lack of funding, however, the only available space he had available for his breeding colonies was in the trunk of his car. His cages consisted of old coffee cans covered with mesh. Try getting this protocol through an animal research committee review!

As mentioned above, this particular strain of inbred mice was important for Ludwik's studies because it showed a high familial transmission of leukemia. Ludwik hypothesized that this was due to a virus. At the time, the primary identification of a virus was that it was an infectious agent that could be passed through a bacteriological filter. There were no readily available electron micrographs, reverse transcriptase assays were far in the future, and immunological assays were few and crude. He spent a great deal of time trying to transmit leukemia with his filtered extracts with a total and complete lack of success.

Discovering the leukemia virus

Ludwik's great breakthrough came in 1951 as a result of his attending a lecture on a virus (coxsackie virus, I believe) that could only infect suckling mice; adult mice were totally resistant. When he went back to his lab and tried his filtered extracts on suckling mice rather than the adults he had been using, he immediately succeeded in efficiently transmitting the leukemia. This was the first demonstration of a virally induced transmissible leukemia in mammals.

This was far from generally accepted, but Ludwik did find some support from fellow researchers: most critically Albert Sabin, a fellow Polish Jew who would go on to develop the oral vaccination for polio.

Eventually the virus, called Gross Passage A, was available to be shipped to other researchers. This virus, which became known as the Gross leukemia virus, was the first mammalian retrovirus to be discovered. Its discovery inspired other researchers to identify many other mammalian retroviruses, many of which were expressed as leukemias, lymphomas, or sarcomas in their respective host species.

Among the first of these were other mouse retroviruses that caused various malignancies in the cells that control blood production, hematopoietic stem cells, and that were also named after their discoverers. These included the Friend, Rauscher, Moloney, Harvey, and Graffi murine leukemia and sarcoma viruses. It should be noted that some of these viruses had acquired cellular genes that conferred to ability to transform infected cells. The existence of these viruses allowed the later discovery of cellular oncogenes.

Fundamentally, these mouse viruses were all close relatives of the Gross leukemia virus that caused leukemia in AKR mice, and were generally passed by vertical transmission, from mother to offspring. This congenital transmission was among the first demonstrations of an infectious cause of cancer. As we now know, there are a great variety of endogenous (carried in the germ line) as well as exogenous (transmitted horizontally) murine leukemia viruses. Many of the above-mentioned leukemogenic murine retroviruses are actually recombinants of endogenous and exogenous viruses, and it was the recombinational event(s) that conferred leukemogenicity.

As mentioned above, some of the recombinations resulted in the acquisition of cellular transforming genes. Within the next several decades, similar viruses were identified in other mammalian species, notably in cats, cattle, and gibbon apes. These viruses, like their murine counterparts, caused a variety of leukemias in infected animals, and the discovery of feline leukemia virus led to the development of vaccines that protect cats from leukemia. Ultimately, Ludwik's work led to my lab's discovery of HTLV-I and –II, the first human retroviruses and (in the case of HTLV-I) the first human leukemia virus. Many of the ideas and techniques developed in this field led to the discovery of HIV and its implication in AIDS. Ludwik's work was thus foundational and highly consequential.

Polyoma virus

In the course of his work on murine leukemia viruses, Ludwik discovered a second tumor virus. His discovery of the mouse polyoma virus came about when he noticed that inoculation of some of his extracts, rather than resulting in leukemia, caused carcinomas and sarcomas of the salivary gland. Heat treatment caused loss of the leukemogenic factor, but not of the salivary gland tumor factor, establishing that it was due to a different virus. Also, the leukemic agent could be pelleted by centrifugation under conditions that left the salivary tumor agent in the supernatant, indicating it was a smaller virus than the leukemia virus. This virus was later named polyoma virus by Stewart and Eddy, because it caused a variety of different kinds of tumors in different animal species. I believe this was the first DNA tumor virus identified in mammals.

Ludwik was thus a major influence on many investigators who came later. However, there was a considerable and quite persistent resistance to the idea that viruses could cause cancer. The controversies didn't end early, and throughout the 1950's he became the subject of some ridicule. Admittedly, his experiments were not always rigorous. They were not always perfectly clean, as some critics said. But he turned out to be correct in the end. His discoveries were never totally out of the question, and the lack of rigor, as we now call it, was in large part due to the lack of advanced technologies.

In retrospect, it is somewhat hard to understand why there was such strong resistance to the notion that there could be an infectious etiology to some cancers. I suppose it stemmed in part from the view that infections were something that occurred rapidly and were relatively transient. Microbes were either cleared by the host or else killed the host, and there was little awareness or appreciation of slow or chronic infections and what might be their effects on the host.

Ludwik also made a number of important contributions to our knowledge of tumor immunity and immune tolerance. His basic hypothesis was that tumor cells expressed antigens that were not expressed by normal cells. Following his earlier studies in France on the possibility of vaccination against transplantable tumors, he used implantable methycholanthrene-induced sarcomas introduced into inbred mice to demonstrate that the injection of small numbers of the tumor cells was able to render the recipient mice resistant to subsequent challenges with large doses of the same tumor cells. These experiments were one of the early foundations of the field of tumor immunology.

Ludwik is the forerunner and father figure for much of the field of retrovirology. Everyone knows the story of Peyton Rous and his discovery of the Rous sarcoma virus (RSV), in the early part of the 20th Century. RSV produced sarcomas in chickens in a laboratory setting and, RSV was among the first viruses ever discovered. This virus was subsequently shown to transform fibroblasts in culture. As such, it ultimately led to important advances in our understanding of in vitro neoplastic transformation as well as a Nobel Prize for Rous some half of a century later, in 1966.

Lasker Prize

Ludwik was recognized for his seminal work by being awarded the Lasker Medical Prize in 1974, along with Howard Temin, Sol Spiegelman, and Howard Skipper, but he was never to be awarded a Nobel prize. In spite of this, the work that established the importance of retroviruses in animals really began with Ludwik, and certainly his work was essential to discoveries that came later with respect to human retroviruses.

Ludwik was an incredibly humble and unassuming man. One day in Cambridge, Massachusetts at a lunch break during a scientific meeting, Max Essex (himself one of the pioneers of the feline leukemia virus field) and I were discussing the new era of biotechnology, the heavy involvement in research of biotech companies, and the fact that many scientists were making a lot of money from their research. This was sometime around 1980. We spotted Ludwik walking up the street, and Max said, “Maybe we should ask old LG what he thinks.” When we asked him what his thoughts were on this, Ludwik answered “Companies, money, I don’t understand. I have everything a man could want.” And he named his blessings in order. “I have my work, I have my car (he loved to drive and go anywhere, and he never forgot that a car ride allowed him to escape from the Nazis), I have my television set (he was a big Perry Mason fanatic), and finally I have my wife.” It was amazing that someone as driven as Ludwik could be that self-effacing. In some ways, I thought it was one of the simplest yet profound statements of personal philosophy that I’ve heard.

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