The Making and Missing of Discoveries:  
An Autobiographical Essay

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Prolog

While progress in science sometimes results from the insight of a genius or from serendipity, more often it evolves from the toil of a vast number of investigators, each building upon another's contributions. Most of these investigators become casualties of progress; the stars of one era fade into oblivion in the light of the new knowledge in a new era. Only historians remember.

In this autobiographical essay, I shall mention successful toilers, those I have known closely or have seen perform, some of whom made history over the past half century. Some were giants. They include three individuals whose wisdom attracted and kept me in experimental medicine. From two, I learned that it is a greater pleasure to give than to take. From them I received. From the third, I learned the strategy of research.

Research is intoxicating, the more so if one sees its application to human disease. I became addicted. Success in research is like gambling: some success brings more of it, but the game can also bring grievous losses. It is the net pluses that count. My failures may have exceeded my successes. I recall remarking to a colleague on one occasion, "If failures are assessed, I may gain the championship."

Let me tell my story as faithfully as I remember it, without gilding or censoring. Since I have been honored by two biographies (1, 7), this article shall be limited to the highlights of my peregrinations in medical research; these covered eight universities and two research institutes. I shall relate the events more or less in chronological order. My peregrinations began with research in microbiology, from there to immunology, virology, hematology, and radiation biology, leading to the multidisciplinary science of oncology. Cancer research, as I recall, was an unattractive infant and did not seem very respectable as a specialty. During the past half century it has grown both in attractiveness and in respectability.

Becoming a Student of Medicine. Learning the Love of Learning

My decision to study medicine at the outbreak of the first world war in 1914 was not accidental. I did not want to be forced to shoot human beings. In school some of the courses were very attractive and I made A grades in these. Other courses were not so attractive and I barely passed these. Two semesters of medicine at the University of Budapest were followed by 2½ years of military service, most of it spent in Russian war prisons, leaving ample time for meditation and the shedding of narrow patriotism. The turmoil of revolutions in 1918 landed me in the (German) Charles University of Prague. Following attendance of an in-depth course on the new science of immunology, given by Edmond Weil, I became his privileged student with residence in the Institute of Microbiology and Hygiene. Here I developed both a love of research and a deep attachment to my dedicated seniors.

Under the direction of Weil, I completed several definitive publications. All were inspired by him, but he did not permit me to acknowledge his guidance properly. These studies dealt with the question of whether antigenic determinants would characterize bacterial species and explain the nature of evolution. The papers that resulted were on immunological (receptor) analyses of microorganisms and mutational studies of the typhoid and paratyphoid groups of microorganisms.

During these studies, the agar plates were kept at room temperature for 1 to 2 weeks for characterization of the mutant colonies. It was common for fungi to fall on the plates, and I noted that where the fungi grew the bacterial colonies were stunted. I thought that the "damned fungi" were depriving the bacteria of nutrients. The possibility that the fungi secreted a bactericidal substance did not enter my mind. A few incidents remain fixed in one's life. This was one of them: seeing myself inspecting the agar plates in search of mutants.

Concurrently, under the advice of the then Dean and Chairman of the Department, Oscar Bail (famed for his discovery of aggressins), I conducted research on the bacterial viruses just discovered by D'Herelle. The nature of the bacteriophage was frequently discussed. I recall Bail saying, "Mark my words, this may be the greatest discovery of our period." He urged me repeatedly to write up my novel observations on D'Herelle's viruses. I did not do this. His idea relating D'Herelle's agents to genes of bacteria seemed fantastic to me. Testing one alternative hypothesis as to the nature of these agents backfired. I prepared several grams of lyophilized bacteriophage by methods of enzyme purification and gave them to Professor Bail as a Christmas present. His comment, "You can do this to many living organisms," was chilly, though correct.

One of my findings survived: the introduction of the agar plate, now a standard procedure, replaced the tedious broth culture technique. It enabled me to give within 48 hr the content of both pathogenic microorganisms and diverse bacteriophages in the feces submitted to me for bacterio-
logical diagnosis. Professor Bail graciously gave me credit for the introduction of the plate technique. (I have been trying for years to locate this reference.)

During those years, I encountered only hints of the then dormant cancer research. One example was the possible recognition of tumor cells shed into CSF. CSF examinations were channeled to me by the University Hospital to be done under the direction of Edmund Weil who made some remarkable and novel contributions. One I recall was relating CSF to diseases of the brain by quantitating the passage of serum components, including normal antibodies, into CSF.

Weil, an investigator of Nobel Prize caliber, died in 1922 at age 45 of typhus fever contracted while investigating the still mysterious immunological identity of Proteus OX19 with Prozvcek’s rickettsia of typhus fever. His senior associate and successor, F. Breinl, also died of typhus. I, his youngest helper, escaped with a high but transient febrile infection probably due to typhus fever. Of Weil’s many original discoveries, perhaps that of the double antigenic and biological character of certain microorganisms (known as rough and smooth) is most fundamental. My research was a segment of his theme. He was a highly cultured, fearlessly honest, and inspiring man with limitless generosity. Shortly after Weil joined the large (over 20) “Gallery of Martyrs” of Charles University (a designation applied to those who died of diseases contracted during research or service), I took a year’s leave of absence from my department.

Intermezzo. Clinical Residency

Following my graduation and the shocking death of Weil, my first mentor, I faced two questions: whether to remain in the laboratory or to turn to clinical research, and what was the future of Europe. My colleagues named three outstanding German university departments of medicine: in Munich, Berlin, and Breslau. Professor Bail made arrangements with Professor F. Kraus of Berlin, where my residency was divided into three parts: clinic (outpatient service), wards, and research. I liked and admired the splendid organization of the clinic but was disappointed by the poor caliber of clinical research and shocked by the poor state of therapy. A physician could do barely more than a wise clergyman. One clinical trial I witnessed resulted in the patient’s death.

The outlook in Europe was grim. “No, no, never” was the motto in the dismembered Hungary. Germany, too, was beaten down and the spirit of revenge was in the air. The United States had turned to isolationism. Since I had been an officer in the Austro-Hungarian army, both Czechoslovakia and Hungary could call on me for military service. My decision was unequivocal: on to the United States and back to basic medical research.

A Microbiologist and Immunologist at the University of Pennsylvania (1924–1926)

Thanks to my publications from Prague, I had several opportunities in the United States, of which the offer from Eugene L. Opie at the Henry Phipps Institute of the University of Pennsylvania was the most appealing. I found in Opie a mentor equal to Weil. Not only did Opie guide my work without accepting credit, but he taught me the language of my second adopted country.

Although none of my own work was concerned with cancer research, it was a frequent topic discussed at our weekly “journal club,” invariably chaired by Opie, whose cryptic comments were gems of wisdom. On one occasion I “defended” the work of Peyton Rous on avian tumor virus when a colleague approvingly reviewed an article denying the existence of this virus, attributing the “takes” to cells passing through silicious filters. This was one of two occasions when, by contradicting a colleague in an open meeting, I lost an influential friend. At another journal club meeting, when I favorably reviewed an article claiming that Hodgkin’s disease was due to a virus that causes encephalitis in rabbits, a mere smile of Opie’s indicated his doubt. When I pressed him for an explanation, he replied that many agents causing this disease had been reported; while he had seen errors in none, all had turned out to be false. The “virus” in question turned out to be extracts of normal eosinophilic leukocytes. The etiology of this disease is still a puzzle. Years later, the concept gradually crystallized in my mind that Hodgkin’s disease goes with lowered immunological resistance (as indicated by lymphopenia), hence the many organisms isolated from it, including tubercle bacilli. The latter led our famous oncologist, J. Ewing, to conclude that “tuberculosis follows Hodgkin’s disease like a shadow.”

I have only one joint publication with Opie (8). This was a surprise reward for a suggestion on how to obtain further proof for his concept of the basic mechanism of the type of anaphylaxis he termed “reverse passive anaphylaxis.”

During this period with Opie at the Henry Phipps Institute, my studies deemed worthy of publication were on the immunological relationship of acid-fast organisms, antigenicity of lipids, and the creation of new antigens by heat. The last study was undertaken at his suggestion after I dogmatically denied this possibility. “Why don’t you try it? Zinsser found it possible,” was his advice, which, as usual, was correct. Dr. Karl Landsteiner asked for a reprint of my report and expressed interest in my joining his staff at the Rockefeller Institute, which I joyously did with Opie’s support.

Learning the Art of Medical Research. Two Years at the Rockefeller Institute (1926–1928)

Landsteiner had been a friend of Weil who had referred to him as the “Dean of Immunologists.” I was eager to observe this master. When he accepted me as an assistant, he stated, to my surprise, that I would have a choice of problems but that he would be senior author of all publications. Two years later when I resigned, I was equally surprised that he made me a senior author on a study that was a biochemical extension of my work on the typhoid-paratyphoid group of microorganisms, which I could not have done without his guidance.

The two years at the Rockefeller Institute were the highlight of my peregrinations in experimental medicine. What I learned there was infinitely more than what was published. Landsteiner was a superb strategist. As he stated, there are...
two kinds of research: one that is likely to succeed and will give you your daily bread ("anybody can do it"); and the other that aims at solutions to great biological riddles such as the basis of evolution. One great contribution in a lifetime is worth the efforts against great odds. Landsteiner said most great discoveries he learned about during his lifetime were considered unlikely or impossible before they were made. Accordingly, more than half of my time was taken up with such studies, including an attempt to transform saprophytic water vibrios to cholera vibrios and to transform one Drosophila strain to another. I also worked with typhoid-paratyphoid-like organisms. Similar studies, systematically pursued by Avery and his associates using pneumococci, ultimately led to the discovery that nucleic acids were carriers of genetic information.

What made my two years at the Institute such a superb learning experience was the contact with many great scientists at lunch, at seminars, and at other times. Landsteiner was interested in all riddles, including that of cancer. He brought with him to the United States a bucket of highly carcinogenic tar of which Peyton Rous made good use. I recall my contact with Rous and James Murphy, both brilliant contributors to cancer research but mutually incompatible. Both were great men, but not without human frailty.

Alexis Carrell, who received the Nobel Prize for his tissue culture work, was isolated and unpopular. I never learned who, if anybody, gave him the suggestion to try in vitro carcinogenesis. Carrell aroused my interest in tissue culture techniques, and I have been making use of them ever since. At the Institute, each department kept away from problems tackled by other departments. (Simon Flexner was a master in selecting life members and keeping a balanced order among them.)

I did not accept Landsteiner’s offer to stay and take over Philip Levine’s work on minor subgroups with added assistance (tackling the individuality and related problems). This work appeared to me to be too mechanical and I was restless to return to independent work. My work with Landsteiner on blood relationships in anthropoid apes attained its prime objective, indicating the differences among blood groups of man and all anthropoid apes, but was to “thin” for publication. Now that Philip Levine has attained greatness among them.)

Becoming a Leukemologist (1928–1932). Entering Cancer Research by the Back Door

In 1927 times were ripe for experimental studies of leukemia, but it called for a man like Opie to recognize the possibilities and to accept a generous grant from Mr. E. Mallinckrodt, Jr., only after a study of the literature on leukemias occurring in animals had convinced him that human leukemia problems could be tackled by experimentation with animal leukemias.

The beginning was frustrating: having the funds, disclosing the plans, and failing to get leukemic mice from those investigators who had them, two of whom became “competitors.” A letter to V. Ellerman (the discoverer of the chicken leukemia virus) was returned: “Deceased. Viruses lost.” During those frustrating years I vowed that if I ever succeeded in developing leukemic strains of animals or isolating leukemia viruses, I would share them with others who wanted them. After several years of hard work, our primary objectives were attained, thanks to several colleagues who offered a helping hand and to the steady counsel of Opie. Mr. Mallinckrodt asked for no reports and required only that his name should not be disclosed. (He relented on the latter some 30 years later, upon the request of Opie.) With initial success other foundations joined in supporting us and the mounting number of competitors.

Several independent approaches were followed simultaneously. One was to develop leukemic mice by genetic inbreeding of leukemia occurring spontaneously in commercial strains or induced by ionizing radiations. The idea of inducing cancer by ionizing radiation was inspired by a report on the frequent occurrence of leukemia among the pioneer roentgenologists. Grafts in isologous hosts were anticipated to indicate whether leukemia was uncontrolled hyperplasia or neoplasia. Transmission by cell-free material would indicate causation by virus. The second approach was to try to obtain a virus from the various types of avian leukoses, to study their character in relation to mammalian neoplasms, and to apply the techniques to isolation of a mammalian virus.

The first approach led to the development of Ak mice and proof that leukemia was a neoplastic disease, genetically transmitted, its expression being dependent on a thymic factor yet to be identified. Lymphosarcoma was experimentally proven to be a form of leukemia localized by antibodies against leukemic cells. This was done mainly by preirradiation of host animals with immunodepressive doses of X-rays. However, the diversity of leukemias, including ability to invade the blood, is also influenced by the character of the neoplastic transformation.

Years later when in Prague, I revisited my old teacher of pathology, Anton Ghon, and related these findings to him. Ghon was a scholar of the malignant lymphomas. He acquired lasting fame for his discovery of the major difference between primary (first infection) and secondary (reinfection) tuberculosis. He admitted that lymphosarcoma was a neoplastic disease, but not leukemia. “Herr Kollege, das kann nicht sein!” was his opinion. Now, reading about newer observations, I admit that some leukemias may be mere hyperplasias. The difference is major from the standpoint of therapy.

Leukemia research led to other types of cancer research. The growing number of excellent competitors led us to turn to these. In leukemia research the outstanding newcomers included Ludwik Gross, Lloyd Law, and Henry Kaplan. Gross brought solid proof for the existence of a leukemia...
I became a mere "kibitzer" to Gross and other colleagues. I recall identifying for Gross the "neck tumor" he discovered among his leukemia passages as a salivary gland tumor due to another virus. It was simultaneously discovered by Sara Stewart, who properly identified this highly antigenic, infectious, multipotent DNA-containing agent, naming it properly polyoma virus. My partner G. Edwards identified it in the nuclei of cells. Several leukemia centers arose in Europe; the competition with them was cordial.

The Ak mice, distributed freely, became a popular object of study. In my study at home is a set of bookends with two carved Ak mice crawling on them (Fig. 1). They were made by a Cherokee whittler, a farewell gift from my colleagues at Oak Ridge National Laboratories, given with the statement that the Ak mice would long survive me. The December 1974 issue of Jackson Laboratory Notes lists some 200 articles on AKR mice published during the preceding year.

Ak and other types of leukemias were used by my associates (L. Reiner, C. Flory) in chemotherapy research prior to the discovery of folic acid antagonists and were taken up by C. Rhoads while at the Rockefeller Institute. After the second world war, he initiated a broad program of chemotherapy at the Sloan-Kettering Institute, initially utilizing our various types of leukemias.

NIH established a committee (on which I served for a short time) to explore all avenues of both clinical and laboratory investigation to energize chemotherapy research. The success attained by the clinical center of NIH; large cooperative groups; investigators, such as G. Hitchings, at pharmaceutical houses; and research institutes, such as that directed by H. Skipper and F. Schabel, was beyond my expectation.

In radiation leukemia, Henry Kaplan made remarkable advances. Even more startling to me was the work on genetic inheritance of murine leukemias by R. Huebner, W. Rowe, G. Todaro, and others and the biochemical research initiated by H. Temin, D. Baltimore, and S. Spiegelman pointing to causation of leukemia (including that of man) by a virus and the elaboration of the role of immunological components in its pathogenesis made by others. These investigations were at a level of sophistication I had not believed possible. They remind me of the comment made by Peyton Rous a few years ago that he did not recognize his virus in what is now being done with it. Such is the law of science. I suppose one should rather rejoice in having taken some part in the evolution of knowledge than become depressed by having missed the potentialities of an area of research that was abandoned.

We succeeded in isolating five different types of avian leukosis viruses: some producing leukemias (erythro-, myelo-, or lymphoblastosis); some, various types of sarcoma; or both. Our Virus 5 produced neurolymphomatosis (fowl paralysis), now known as Marek's disease. It is similar to the Epstein-Barr virus which is associated with Burkitt's lymphoma of humans. An early noteworthy finding was the spontaneous transmission of avian leukosis by blood-sucking insects (Herbert Ratcliffe); another, the discovery of the presence of the leukemia virus in very high concentrations in sera of leukemic chickens. After the development of the high-speed centrifuge, we (and Elvin Kabat) sedimented this virus into a good-sized pellet, whereupon, greatly excited, we rushed to sediment sera of leukemic patients. No pellet was formed. The chemical composition of the pellet from avian blood was about the same as reported by a colleague for the leukemia virus. Pursuing this finding led first to detection of highly sedimentable material in diverse

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4 The suffix "R" stands for the Rockefeller Institute, where Clara Lynch "nursed" the Ak mice during the second world war and named the strain AKR.
organs with some immunological specificity and later to concentration of Gross virus from the blood of leukemic mice. In the analysis of pellets of avian myeloblastosis viruses, Joe Beard had notable success.

With Evans Stubbs (Professor of Veterinary Pathology), we studied all types of leukemias in domesticated animals. One of these was the still-mysterious venereal sarcoma of dogs which is transmitted by intercourse and can regress. One animal recovered spontaneously, while her tumor, grafted on other animals, killed the hosts with widespread metastases. Our avian leukemia viruses were kept in deep freeze during the second world war but were lost after my migration to Texas. History can be cruel to those who do not follow through on their initial success or who fail to pass on their hard-won material to succeeding generations.

With my move to Cornell-New York Hospital Medical Center with Opie, my activity but not my interest in leukemia research began to decline.

Practicing the Triad of Academic Pathology: Service, Teaching, and Research (1932–1947)

At Cornell-New York Hospital, I ceased to be a full-time investigator and became a disciple of the Cohnheim-Welch-Opie school of experimental pathology. My three mentors (Weil, Opie, Landsteiner) were all pathologists, broadly based biomedical scientists to whom experimental pathology was synonymous with experimental medicine. I recall the words of Landsteiner: "Whatever major contribution I may have made originated from an observation made in the practice of pathology." I was not so fortunate, but two or three minor papers were based on interesting anatomical findings.

I performed a few hundred autopsies and checked a larger number done by others. My aim has been to learn from the postmortem examination the "life story" of the patient, the innocent as well as the major changes leading to death. At the outbreak of the war, I spend two months of intensive study in Latin America under the auspices of the American College of Physicians and Surgeons. While in Costa Rica, I made rounds with the staff in the morning and performed autopsies in the afternoon. There I learned of our diagnostic ignorance of diseases in underdeveloped and subtropical countries. This led to some unforgettable blunders.

At Cornell my major assignment was teaching experimental pathology. Under Opie, some investigative work was compulsory for all students in the pathology class, a vanishing exercise. Groups of students had the choice of working during two semesters on up-to-date research problems listed by the staff or proposed by themselves; they reported their results before the class. Many class experiments were related to cancer and several resulted in original publications. This exercise attracted some students to investigative medicine and made many others better practicing physicians. Many continued their research until—and some, even after—their graduation. To commemorate the spirit of experimental pathology as advanced by Opie, I wrote up its history and the achievements of teaching experimental pathology in the Opie memorial issue of the Archives of Pathology (2).

My triple responsibility quadrupled when I became acting chairman of the depleted pathology department, an all-around thankless job. Several members of our staff, including Opie’s successor, departed for the Pacific coast with the New York Hospital unit. This created havoc with my leukemia research begun at Penn. I lost "priority" in investigations on the role of the thymus and other problems pertaining to leukemogenesis to my splendid competitors, Lloyd Law, Henry Kaplan, and others. Advancement in rank, the impending and actual retirement of Opie, and duties assumed under the Surgeon General created a strain on my multisided activities. The acting Surgeon General, Stanhope Bayne-Jones, a clear thinker in the field of microbiology, was co-founder and editor of CANCER RESEARCH. When, at the outbreak of the war, I asked "B-J," "What about cancer research?" he urged me to carry out the basic part of it. I did, but with grievous losses.

During this most crowded period of my career, high priority had to be given to teaching and service; we omitted writing up in detail experiments on the genetic inheritance of the virus causing Ak leukemia, on the role of thymectomy in preventing viral expression, and on the use of thymus grafts to activate the expression of virus. Although I did summarize them in 1946 in the first issue of the obscure Journal of Gerontology (3), it is natural that most credit for these developments is given to others. Our finding of the genetic inheritance of leukemia in Ak mice would have been a complete "casualty of progress" were it not for R. Huebner’s reference to it as an integrated "proto-virus." The term "proto-virus" proposed later by H. Temin is perhaps better. My preference would be "protoleukemia virus."

My assignment with "B-J" met with some success, however. In a routine test for respiratory viruses, we isolated a new member of the psittacosis-ornithosis-like agents from the lung of a patient who died of pneumonia. She had been exposed to pigeons. Preserving a fraction of the pneumonic lung in the frozen state enabled us to prove solidly the causal relation of this agent to pneumonia. This experience aided in our advocacy of the establishment of tissue banks for various purposes, including preservation of cells in the living state. In the course of a class experiment with L. Gahagan, the "blind passage" technique was successfully put to use for isolation of a pneumotropic virus latent in our colony. Publication of the experiment was delayed until C. Niggs reported on isolation of the same virus, which correctly carries her name.

The committees on which I served during and after the war, under the Armed Forces Institute of Pathology, the Atomic Energy Commission, and NIH (on the latter, from its inception until recently), were "give and take" affairs. Such experiences broaden our horizon and make us more catalysts than doers of research. My past experience in microbiology, immunology, radiation biology, and cancer was advantageous in performing these services, but performing these services limited the time I could devote to my own research.

As I reflect on my turbulent 15 years at Cornell, they were fairly productive due to a good student body, associates, and assistants. We reported on the individuality of various types of leukemias in mice; their transmission by a single
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cell; a method for preservation of living cells by slow freezing (with C. Breedis); genetics of spontaneous leukemia (R. Cole); the role of the thymus in leukemogenesis; the individuality of the monocytes, histiocytes, and microglia cells (with H. Dunning) and their relation to reticulum cell sarcoma; differentiation of leukemia and leukemoid reactions (with Bill Barnes); and the possibilities of experimental chemotherapy of leukemias (L. Reiner, C. Flory). We also enhanced the list of different viruses causing leukemias and sarcomas and indicated the essential identity of mouse and human leukemias and the neoplastic character of both.

There is one aspect of viral leukemia to which I have never given up returning: the knowledge of factors, such as those residing in the thymus, which can activate a genetically integrated virus. I believe that a pathogenic or saprophytic virus can be genetically integrated. They can remain harmless, possibly even beneficial, until some factor activates their expression. This assumption is solidly rooted in the investigations of H. Temin, D. Baltimore, and S. Spiegelman. Although several workers have reported on thymic hormones, none thus far described has the capacity to activate the latent virus of thymus-dependent leukemia. Our last publication (in 1966 with H. Ioachim) suggests that it is secreted by the thymic epithelium, but more recent research points to the versatile T-lymphocytes.

The two years Elvin Kabat spent with us at Cornell were highly productive. In addition to work on high-speed sedimentation of leukemia viruses, his work included histochemical identification of alkaline phosphatases. The localization of alkaline phosphatases in the proximal convoluted tubules led us to identify the site of nephrotoxic agents, such as the mercurl Compound then used in the therapy of syphilis (C. Breedis).

While under Opie, I had dreamed of chairing a department of pathology somewhere in the Cohnheim-Welch-Opie tradition. When I was bypassed after his retirement, it seemed less likely that I would attain such a position. Thanks to a reorganization of the Veterans Administration, I found a new home in Dallas, Texas.

Practicing the Triad of Pathology in Dallas (1947–1949)

The Southwestern Medical College was affiliated with the Veterans Administration Hospital in Dallas. I became associated with both. The excellent medical faculty of this university wholeheartedly accepted me, but the dean (a retired general of the Army Medical Corps) refused to give me full professorship (the title held at Cornell); nor would he accept any research grants from the foundations that had supported me in New York and offered to extend their support to Dallas. However, the Veterans Administration generously made special allocations for continuation of my research. The staff of the university also encouraged me. Tinsely Harrison, Professor of Medicine, consoled me, saying that he himself had been considered a foreigner when he came to Dallas (he was a Harvard trainee, born in Alabama), but added: "When the Texans will know you, they will like you and you will like them." (He was right.)

Some notable observations were made in Dallas (with T. Bali) on diverse nonfunctional and functional radiation-in-
duced ovarian tumors (their isolation and the specific normal mast cells that later led us to the isolation of a highly functional mast cells. Unfortunately, the aggressive ser-
vice, including supervision of hematology and other units of the Dallas hospital and elsewhere in the Veteran Administration's Southwest Division, left little time for research.

The most common neoplastic disease encountered among the male population of the Dallas Veteran Administration Hospital was lung cancer, linked to cigarette smoking. The most instructive parts of my service were the clinical-pathological conferences, held jointly with Tinsely Harrison, a scholarly clinician.

When its regional organization was abolished, the Veter-
ans Administration offered me the choice of chairing the laboratory service of another of its excellent university-affiliated hospitals. At the same time a cordial invitation came from Alexander Hollaender to join the Oak Ridge National Laboratories, which I accepted following consulta-
tion with Shields Warren, a trusted statesman in the Amer-
can scientific world. So ended my second period as a broadly based pathologist.

Adventures in Radiation Biology at Oak Ridge National Laboratories (1950–1954)

The invitation to join Oak Ridge National Laboratories was a bonus received for the research on biological effects of radiations prior to learning about the consequences of the atomic bomb. It began with induction of leukemia by x-rays (1929–1932), followed by the discovery of ovarian and other tumors as a late effect, and attempts to cure leukemia by external gamma radiation. The latter led to the conclusion that external radiation cannot destroy all leukemic cells without killing their hosts. Rescue of animals from lethal irradiation by bone marrow transplant was a later develop-
ment. Since then, I keep dreaming of a project to establish deep-freeze storage banks of bone marrows of normal people for possible use later in their lives or, better yet, to try to grow their marrow stem cells and freeze these away.

While at Cornell I accidentally fell into the area of radia-
tion neoplasia. I was unaware of the gigantic developments in radiation physics that had brought Nobel Prizes to a succession of scientists (of the 22 Nobel Laureates to 1948, 11 were radiation physicists) and had remained ignorant of these while teaching radiation pathology at Cornell. In Hollaender’s splendid Biology Division, I was brought up to date by taking a course in radiation physics and I learned about the many-sided problems it presented to radiation biologists.

Aided and guided by members of other sections of the Biology Division, I was able to make a thorough study of several problems and to analyze the hormonal conse-
quences of the ovarian tumors that I carried with me from Cornell. (The granulosa tumors produce hypervolemia with anemia: the luteomas cause hypervolemia with erythroemia. Both were quantitated by isotopic techniques.) A few of our observations remained unpublished (for example, the "im-
possibility" of killing mice with 4C). Others, notably the role of hormones in neoplasia, opened avenues of research that
have been keeping me busy ever since. The breakthrough in this direction came from an analysis of Gorbman's reports that $^{131}$I induces tumorous changes in the pituitary, which he attributed to "stress" or radiation. Our studies led to an incrimination of a derangement of the thyroid-pituitary axis, demonstrating how this can be manipulated to produce at will either thyroid or thyrotropic pituitary tumors. J. Dent performed a critical experiment, induction of thyrotropic pituitary tumors in mice by surgical thyroidectomy done under binocular microscope, leaving behind a parathyroid.

Having learned about thyroid-thyrotrope homeostasis, we raised the question: What is the nature of the pituitary tumors that have been induced independently by several outstanding investigators? Transplantation experiments indicated that they were invariably mammotropic hormone (prolactin) secreting. Nowadays, in characterizing a tumor we tend to rely on rapid test tube reactions that are often incomplete or of dubious validity. When puzzled, I turn to the isologous animal host to tell me the character of a given functional neoplasm.

The pathogenesis of the acute radiation death with anemia also puzzled me, as RBC are radioresistant. The appearance of lymph nodes loaded with hemosiderin cells gave a clue. The lymph ducts, which are normally free of erythrocytes, were full of them. Diversion of erythrocytes into the lymph stream, a one-way track, solved this puzzle. (This was missed in the otherwise classical treatise describing the pathology of acute death among the Hiroshima casualties.) But why the diversion? Thrombocytopenia was known to be associated with radiation anemia (E. Cronkite). Within minutes after platelet perfusion, the bloody lymph became clear. An editor of one prestigious journal, prejudiced by some work of his own on permeability of cutaneous lymphatics, rejected our paper, but another journal, Blood, accepted it (9). This was an exceptional experience. Conditional acceptance of a hastily submitted paper was not rare in my life. (Having been on the editorial boards of several journals as endocrinologist, microbiologist, and oncologist, I learned to appreciate the time-consuming job of reviewers, time given freely and anonymously.)

After mastering the preparation of platelet transfusion, I applied it to a patient given supralethal doses of radiation for leukemia. Fair recovery followed, but death from leukemia was not prevented. Our efforts to preserve platelets as we had preserved living normal cells by freezing failed. Platelepheresis is now effectively used to aid patients with platelet deficiency disorders.

When Shields Warren (founder and Chairman of the Division of Biology and Medicine of the Atomic Energy Commission) asked me to take part in a gigantic interdisciplinary study of an experimental atomic bomb explosion, known as Operation Greenhouse, he gave me ample extra support and permission to do anything else in which I was interested with the budget that had been appropriated to my section of experimental physiology and pathology.

In studies of radiation-induced leukemias of various types and the relative biological efficiency of diverse types of radiations, my senior associate, A. Upton, did a "lion's share" of the work. Research on radiation-induced cataracts was so precisely done by two expert practicing ophthalmologists as to serve as a biological dosimeter in amimals subjected to various types of ionizing radiations. In these and other areas of radiation biology, I was mostly a manager or catalyst. So shielded, I was able to expand research in novel directions related to hormonal "politics."

The well-financed, newly funded radiation biology laboratories of the Atomic Energy Commission created tough competition in almost every area of radiation research. In our Biology Division, Hollaender wisely opened a new subdivision devoted to radiation protection in mammals. This and other scientifically attractive and practical radiation-related problems became extremely competitive ("bandwagon") areas. I yearned to return to the free university life. So I welcomed the invitation of Sidney Farber to join his "Jimmy Fund" (Children's Cancer Research Foundation) as his associate director and chairman of the experimental pathology section, with no restrictions on investigation of any area of experimental medicine.

My five years at Oak Ridge National Laboratories were among the most productive of my career. The knowledge gained there came with me and from time to time has been helpful in research unrelated to radiation.

The Harvard Years (1954–1959)

Throughout my career I have been connected with several academic institutions and have had occasion to learn about many others in the United States and abroad. I found Harvard second to none. There I witnessed the practice of academic ideals in which other universities were deficient in various ways. As Clinical Professor of Pathology, I took part, in a limited way, in all academic activities. All the problems studied in my section were related to hormones and neoplasia. If my Boston period was productive, it was to a large extent due to Harvard. Its fame channeled to my laboratories guest investigators from several parts of the world: Australia, England, Israel, India, and Japan. The associates recruited from the United States and elsewhere were all dedicated investigators, as documented by their publications. Two of the guest investigators, D. Metcalf (Melbourne) and N. Haran-Ghera (Rehovot), are among the current leading investigators in cancer research. Members of the Harvard faculty and some from distant places cooperated in major ways. Among the former, I consider outstanding the work of Paul Hagen on the isolation and biochemistry of the heparin, histamine, and serotonin secreted by our mastocytoma. (This tumor is still being requested quite frequently by colleagues.) Similarly, the research of Jean Mayer on obesity of our adrenotropic tumor-bearing mice is still of current interest. Associates of the late G. Pincus, a pioneer investigator of steroids, were my helpful consultants and one (E. Bloch) analyzed the corticoids secreted by mice bearing our adrenal and adrenotropic tumors. Kelly Clifton was channeled to us by Roland Meyer of the University of Wisconsin under whom he did his thesis work on estrogen-induced mammotrophic tumors. Clifton became a senior member of my staff in Boston. Presently, he has double professorship at the University of Wisconsin. Through another associate, A. Cohen, several of our hormone-secreting tumors landed in the laboratory of
my esteemed friend, Gordon Sato, whose tissue culture clones of our tumors are now widely used in diverse types of research. The unique tumors were deposited in the Tumor Bank managed by the Mason Research Institute in Worcester, Mass., under the supervision of D. Jane Taylor of the National Cancer Institute. U. Kim, the last to join my section in Boston, has made excellent contributions in the establishment and analysis of diverse well-defined mammary tumors. He and others too numerous to name have distinguished themselves by original contributions after they left Boston.

A magnum opus while at Harvard, "A Meeting of Ways in Cancer Research: Thoughts on the Evolution and Nature of Neoplasms," (4) was my presidential address to the AACR. Unintentionally, this turned out to be my farewell address to Harvard. It sums up three decades of experiences. Although the critique of one-sided approaches to the riddle of cancer is still valid, I failed to give adequate recognition to chemotherapy and to the contributions made to it by my chief, Sidney Farber.

Sidney Farber's contributions to cancer research were multisided. He channeled federal money to cancer research and gained enthusiastic support in New England for his humane Children's Cancer Research Foundation, dedicated to the total care of children with cancer. Following his success with folic acid antagonists, Farber dedicated his career to cancer chemotherapy.

The events leading to the discovery of folic acid antagonists are yet to be recorded by a historian. I recall the beginning. R. Lewiohn, a retired surgeon of New York's Mount Sinai Hospital, had the idea that since metastases are rare in the spleen, this organ might contain some anticarcinogenic substance. (I gave him leukemic mice to explore this possibility.) He turned to Y. SubbaRow, the Director of Lederle Research Laboratories, to analyze his splenic extract. This led at first to the vitamin biotin, later to folic acid. The discovery of folic acid antagonists was a major breakthrough in chemotherapy. SubbaRow had given folic acid to both Farber and Rhoads for clinical trial. (All three were Harvard trainees.) It was probably Farber who first observed that folic acid aggravated leukemia. Who had the idea to test antifolics I know no more than who discovered the concept of antibiotics. (I thought it was D. Woolley of the Rockefeller Institute, but learned later that it may have been V. DuVigneaud.) Let historians clarify such controversies.

My cordial relations with S. Farber became strained and my compulsory retirement age was close. I informed friends about my desire to leave and the opportunity came with an invitation from Roswell Park Memorial Institute. Years later, Farber invited me to return to Boston and chair his new cancer hospital for adults. Time is a wonderful healer.

At Roswell Park Memorial Institute, Buffalo (1959-1961), and at Columbia University (1961- )

During my two years at Roswell Park Memorial Institute as Director of the Experimental Pathology Section and Professor of Experimental Pathology at the graduate school of the University of Buffalo, I continued, with a small staff and graduate students, some unfinished work begun at Harvard and also started to branch out in newer directions. Inspired by T. Haushcka, I began to turn my attention toward chromosomal changes in neoplasia, especially in relation to dependent neoplasms. We have both continued to be interested in the immunological (histocompatibility) changes associated with neoplastic transformation.

In 1961 two telephone calls invited me to join Columbia's pathology department and to become Director of the Department of Pathology at Columbia's cancer hospital (named after the famous Columbia pathologist, Francis Delafield). This Institute of Cancer Research was founded by a grant from Mr. G. Crocker. I knew it to be an excellent institute while under the directorship of Francis Carter Wood and W. Woglom, pioneering in carcinogenesis by parasites. One telephone call was from Alfred Gellhorn, then Director of the Institute of Cancer Research and Professor of Medicine. Surprised at his offer, I asked whether he knew how old I was. He replied, "You are good for another 40 years." His invitation was followed by that of the Chairman of the Pathology Department, Donald McKay. So I returned to New York, again with the triple responsibilities of service, research, and teaching.

My chief research supporter remained the USPHS, and I have been continuing to serve it in a limited capacity. New York City's Health Department, which financed Francis Delafield Hospital, was generous too, until its financial difficulties compelled it to curtail support of research. The service responsibilities were heavier than I had expected, and in spite of New York City's most liberal retirement plan, I retired from the Francis Delafield Hospital to the Institute of Cancer Research, which became an independent department of the College of Physicians and Surgeons under the directorship of Sol Spiegelman. Dr. Spiegelman allayed my worries about the limitations imposed upon me by age, as had his predecessor, Dr. Gellhorn. Similarly, many newly won colleagues at this medical center became cordial and helpful friends. Following completion of a special building for the Institute of Cancer Research (financed by USPHS and New York City), I moved my small research unit there and gave up service responsibilities altogether, but not teaching, done mostly "on the job."

The last two phases of my career fall into the present, in which you, my readers, are the actors. A discussion of these would be inappropriate. My recent work does not equal in originality that done earlier, but this is in part compensated for by a greater maturity of outlook. Those interested may peruse my Harvey Lecture, "Pituitary Cybernetics and Neoplasia" (5) and my most recent comprehensive article, "Hormones as Etiological Agents in Neoplasia" (6). As to the future, I plan to tackle short-term problems, aided mostly by on-the-job trainees who are interested in the currently neglected area of the biology of neoplasia, and look forward to cooperation with colleagues majoring in different disciplines of neoplasia.

Epilog

After three score and ten, it is a special privilege to be still active at the bench. Although physical and mental activities
decline with age, there are still short-term biological problems anchored to past experience with promise of meritorious contributions, there is the opportunity to guide junior scientists who seek counsel or on-the-job training, and there is time to sum up the experiences of a long, agitated life.

Soon after my arrival in the United States in January 1924, I was cured of youthful dogmatism by a professor of microbiology-immunology who was familiar with my publications. He rightly challenged my technique. (Absorption tests for detection of antigenic differences should be quantitative and cross-reactive of the respective antigens and their antibodies. My tests were not done precisely, a basic error committed by many even today.) But he offered me a position in microbiology-immunology.

I already recognized the vanity of priority problems in the 1920's, but I cannot recall anybody who has completely overcome this human weakness. The collective knowledge accumulated by our scientific ancestors forms the ambiance in which an inquisitive ego broadens its horizon. Even geniuses like Einstein have their ancestors; few create by serendipity. Others, as myself, mature under wise mentors. As someone once said, at a certain state of knowledge some discoveries are inevitable. Whoever reaches the top of a mountain sees what is beyond it. Only limitations of space prevent me from relating the many embarrassing moments when a search of the literature disclosed that somebody "was there before us." It is a cynical, facetious saying that, when you find something highly interesting, hurry to publish it; you may never be able to repeat it. Also, when you find something interesting, don't bother searching the literature; work done in the distant past that is not common knowledge should be repeated anyhow. While the priority bugaboo is a human frailty, its current abuse, aggravated by the present research grant system that pays much attention to quantity and little to quality of publications, is deplorable.

I shall conclude this article with the evolution of my thoughts on the fundamental nature of cancer. The first solid finding pertaining to the character of cancer cells was that of their progressive growth when transplanted in normal hosts in which the number of each cell type is limited by homeostatic forces. T. Boveri is credited with the theory that cancer is due to chromosomal changes attributable to mutation. The discovery that normal cells can grow "unrestrained" in vitro did not abolish Boveri's concept, since the homeostatic restraining forces are absent in vitro. Most biologists, including C. Little (1941), accepted the mutation theory, since the neoplastic changes appeared sudden and were associated with decreased specificity when perpetuated from one cell generation to another. Peyton Rous challenged this concept. Impressed by his in-depth studies of chicken tumors, he arrived at the concept that all neoplasms were viral diseases. Rous' concept had many adherents. At an international meeting in the early 1940's, I naïvely challenged him. I stated that viruses were only one of the causes of neoplasia but was silenced by his brilliant oratory. Although I myself isolated several avian neoplastic viruses, I was much impressed by the equally brilliant discovery of E. Kennaway and his associates of the isolation of nonirritating, highly carcinogenic substances in tar and by studies of radiation-induced neoplasms. I stuck to the mutation theory. If the emphasis in the definition of mutation is placed not on color, size, texture, magnitude of alteration, etc., but on characteristics of any kind acquired abruptly, discontinuously, and retained permanently by a given cell lineage, it should include the neoplastic change. Years later, Rous himself, while working with chemical carcinogens, dismissed his earlier idea that viruses might be the sole causes of neoplasms. Incidentally, these later studies leading to recognition of inducers and promoters and the existence of latent cancer cells surpass in originality his excellent work on tumor viruses.

Having recognized that all types of leukemias and lymphomas are neoplastic diseases, I spent years studying the three classes of carcinogens: chemicals, viruses, and radiations. Studies with carcinogenic substances led to research on the role of hormones in inducing, promoting, or inhibiting the growth of neoplasms. Regulation of cell growth and function is the business of hormones. If they were carcinogens (changers of the genetic code), life could not go on. Yet derangement of homeostasis resulting from sustained hormonal stimulation can lead to autonomous cancers of hyperstimulated cells. This is attained slowly by means of an intermediary change, which Rous recognized (in a situation not involving hormones) and named conditional neoplasia. We recognized the existence of this change in hormonal neoplasia as one that precedes the development of autonomous cancers and named it dependent tumor. The fundamental change underlying dependent tumors is yet to be discovered. It seems to involve a progressive hereditary modification of cells which is still reversible but, which if not corrected, invariably leads to fatal cancer. A good human counterpart of the experimental dependent tumors are the so-called benign metastasizing tumors of the thyroid. E. B. Astwood recognized this and introduced their treatment with antithyroid drugs. Their partial destruction by the earlier standard therapy ultimately attains the opposite effect: enhanced growth of residual tumor cells. Even after they attain autonomy, many tumors are still responsive to hormones. (Such are many human tumors of the mammary gland and prostate.) Thus, hormones can aggravate or hinder induction and growth of many tumors. The hormonal studies led us to recognize a fourth inducer of cancers: spontaneous replication error of DNA (cf. Refs. 5 and 6).

The basic nature of neoplasia is still in the realm of speculation. I shall deal with this in a forthcoming article. Earlier (4), I emphasized the contradictory "theories" arrived at by different basic scientists concerning the fundamental nature of cancer. Solution of this problem calls for cooperation of basic biologists with nucleic acid chemists and perhaps also with crystallographers. It revolves around the identification of genes and their derangements. Their expression is recorded by biologists, who have vastly extended our knowledge by identification of loci of many genes in chromosomes. Their precise localization will be detected by nucleic acid chemists who are investigating the structure of undifferentiated DNA and that depressed (differentiated) by its associated proteins. In the years remaining, I hope to take an active part in the biological aspects of the fundamental nature of neoplasia, which is intimately
related to that of genes, DNA replication and differentiation, and their expression.

DEDICATION. ACKNOWLEDGMENTS

This autobiographical sketch is dedicated to my mentors, including the three mentioned in the text, and many others known in medical history or unnamed, whose aim in life was selfless dedication to the advancement of knowledge.

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