Michael B. Shimkin

Lost Colony: Laboratory of Experimental Oncology, San Francisco, 1947-54: Historical Note 1, 2

Note

Four volumes bound in Government-green are arranged as on left. They record a 7-year period of cancer research, my life, and the lives of several hundred patients and other people. This is the visible residue of the Laboratory of Experimental Oncology (LEO), a collaborative activity between the National Cancer Institute (NCI) and the University of California School of Medicine in San Francisco; I headed this activity between 1947 and 1954. The volumes consist of annual reports, a collection of published reprints, a scrapbook, an album of pictures—and some memories. This collection of four volumes probably is unique. I may be the only one who had read every word herein contained. Dr. Nicholas Petrakis, a legacy from the LEO who remained at the medical school, retained the brass plate from the front door—a relic that undoubtedly will outlast the papers. Yet the experience, as an early example of a regional cancer center, retains heuristic values, perhaps mostly negative ones.

THE LAUNCHING

A constellation of occasions and circumstances differentiated into the LEO. After 8 years at the NCI and war service with a parade of acronymic agencies (OSRD, UNRRA, SHAPE, and WHO), I wanted to settle down in an academic environment and contribute to the solution of the cancer problem. Surgeon General Thomas Parran agreed to such an arrangement and even edited an exploratory letter that I drafted to Dr. Francis Scott Smyth, dean of the University of California School of Medicine in San Francisco, my alma mater. Dr. Roscoe R. Spencer, director of NCI, was favorable to the concept of colonies and also encouraged me.

One of the members of the National Advisory Cancer Council in 1946 was Dr. Robert S. Stone, professor of radiology at the University of California Medical School in San Francisco and a medical director in the Manhattan Project. He heard about me from his academic associates and from my involvement with an extension of the Manhattan Project at the NCI. Dr. Egon Lorenz, who was studying the lifetime effects of low levels of radiation on several species of rodents, was having difficulties with the pathologist assigned to him for the hematologic work. I was asked to take over; in the process, I learned some hematology.

One day I was asked to meet Stone. We chatted, and I expounded my ideas on a well-supported combined clinical-laboratory unit on cancer research in an academic environment. I wanted to demonstrate that biomedical research programs of the National Institutes of Health (NIH) could develop as colonies of full partnership with universities and that such research should be pursued by full-time research teams. Stone was interested, and careful. The dean and his cancer committee were in favor, he said, but no money, no space, no academic positions were available.

Despite these discouraging words, an exchange of letters between the president of the University of California and the Surgeon General of the Public Health Service formalized an agreement. A sum of $40,000 was allocated from the budget of the NCI, and negotiations for space were on the way in San Francisco. Dr. Howard R. Bierman, about to leave the Navy, appeared on the scene via an introduction by Spencer. He was a graduate of Washington University in St. Louis and an enthusiastic physiologist who was taking out a patent on a new strain gauge (f). He appeared to be a good man around whom to develop clinical investigations, and a civil service position was obtained for him. He proceeded ahead of me to San Francisco, where I arrived in January 1947.

Space for LEO was found at the Laguna Honda Home, a facility for the aged poor of the city's Department of Health. It was a castle housing some 1,500 souls, whose average age was over 85. The name, meaning "deep lake" in Spanish, was derived from its proximity to a water reservoir about 3 miles south of the medical school campus on Parnassus Hill. San Francisco's director of Public Health, Dr. Jacob Geiger, was an old Public Health Service officer from the plague days in California, a big, pleasant diplomat with a hobby of gathering medals. He, the dean, and the director of the Public Health Service district compiled the necessary documents of agreement, and for the rent of $10 per year we acquired two floors of one wing of the building. The upper floor was to house the clinical beds and facilities; the lower floor was for the...
basic laboratories, physiology equipment, and animals. Immediately, we ran into long discussions with the administrator of the building, who was not at all sure that racers and mice were included in the agreement. The administrator was a dedicated man with much time on his hands, and discussions with him were interminable.

Contracts were let via the medical school for construction in our area, and reimbursement from the NCI was arranged by one telephone call. Surplus laboratories and office equipment accumulating from demobilization was easily procured, and we were soon sufficiently equipped. By summer we were in place. Surgeon General Parran dropped in to give his blessing.

The basic staff was quickly assembled. Among the earlier additions were a biochemist, Dr. Bernard Schacter; an M.D.-Ph. D. immunologist, Dr. Leo Melcher; and a physicist, Mr. Bruce Shumway. But most important were two indispensable women who really ran the place: Miss Dorothy Messee, chief administrative assistant, and Miss Marjorie Brown, chief nurse. By the time the facilities were completed in June 1947, 15 people were on the staff.

Meanwhile, Bierman and I were making clinical and academic contact in the area, including seeing a few patients on consultation. One was a man with a disseminated lymphosarcoma, with external nodules covering his whole body. We had amsul of nitrogen mustard and gave the patient one course. Every nodule disappeared and the terminal patient sat up and demanded food. News of the miracle, which unfortunately lasted but a short time, spread through the city.

We had meetings with the cancer committee, a consultative cancer board was reorganized, and Bierman was put in charge of the NCI cancer teaching grant to the medical school. With a statistician hired for the purpose, plans were started to devise a national test of cancer knowledge among medical students.

The laboratory reported to the medical school and to the NCI. As good as bad consequences came from having more than one bureaucracy to work with. Printing of forms and announcements, for example, was proscribed by Government regulations but simply achieved via the university. Travel to meetings was difficult to finance by the university, but at that time easily arranged with the NCI. Such alternate arrangements were made possible by our several sources of funds.

The basic allocation was from the direct operations budget of the NCI; we were, in turn, a “branch” of their structure, loosely placed in the office of the director. The experimental ward was financed by an NCI grant, one of the largest at the time, to the medical school; I expended this money by university rules. A small budget was set up for us by the medical school; this was later derived from the all-university cancer appropriation from the State.

The three sources of funds were reflected in three personnel systems for employment. With the exception of Bierman, members of the scientific professional staff were officers in the Public Health Service. Others on the direct NCI funds were on Federal civil service. The clinical help were hired through the university system. The salaries and emoluments differed and had to be reconciled, a reasonable problem for all but the clinical professionals.

The last item was an Achilles’ heel of the activity. I had a fixed idea that clinical investigations should involve no financial arrangements between the patients and the investigators. Thirty years later, I believe this more strongly than ever. The world of the real, even in 1947, however, was out of focus with my beliefs. The medical school faculty derived much of their income from private practice—open, or hidden, or rationalized. I soon found that even seeing patients on consultation and not charging for such consultation embarrassed the physician and the patient.

All services were free to patients admitted to the laboratory ward, and we had no accounting or billing system. Inasmuch as officers of the Public Health Service were “on duty” 24 hours a day, I had control over their activities and allowed none except for one who supplemented his resources by emergency-room attendance on weekends. Such restriction was not applied to civil service employees, whose time after work was their own.

IN FLIGHT

By the end of the first year, the LEO was a fully developed mini-experimental hospital of 15 beds in addition to laboratories for physiologic, biochemical, and immunologic work. The total budget was now $212,000. The staff comprised 9 professional investigators, 12 administrative and technical assistants, 8 nurses, and others for a total of 49 people. Residents in medicine and in pathology were rotated through the facility. I was secretary of the statewide Cancer Research Coordinating Committee of the university, on the cancer...
board, and chairman of the planning committee for a research floor of the new medical school buildings. Giemnian was chairman of the consultative tumor board and of the cancer teaching program for the medical school.

The clinical work was oriented around two internists and required collaboration and participation by many other specialists. Pathology needs were met by setting up a service extension from the medical school, with a full-time technician and resident, thus expanding the Laguna Honda Home pathology services. Radiology needs were initially met by Laguna Honda Home, but required the purchase of a new fluoroscope. For minor surgical procedures, consulting surgeons provided free services; for major surgeries, patients had to be transferred to the University Hospital.

We hoped to develop isotopic radiotherapy and assembled the necessary equipment, including a hood with a collecting device on the roof four stories above. Three research fellows in radiology served with us, but later changed careers to pathology and pediatrics.

The professional staff had clinical appointments at the medical school in experimental oncology, and for administrative purposes they were under the Division of Medicine. We were listed separately in the catalog of the medical school. Our main relation, however, was to the interdepartmental cancer board of the medical school, initially chaired by the professor of pathology but soon replaced by Stone, the professor of radiology. He was a capable radiologist and a pioneer of the age.

Stone was the eminence grise of the cancer situation at the medical school. He enjoyed complete control in his department and volunteered his participation in budgetary and administrative matters of the laboratory. Not having attained this goal, he began to draw up a "constitution" for a Cancer Research Institute (CRI) at the medical school. The rules became increasingly more restrictive and formal, with long hours of acrimonious discussion about specific provisions that seemed trivially detailed.

Finally, I recognized that the planned institute was being set up for Stone as its director, and that I was seen as a competitor for the position. I announced that my role would continue to remain in the Public Health Service and that although the LEO would be within the proposed CRI, I intended to retain control over it whether at Laguna Honda Home or in the new facilities in the medical school. The CRI constitution was soon patched up, and my relations with Stone became formal. The medical school obtained a building grant of $1 million for an extra floor to house the LEO. Stone decided not to become the director, and instead a pathologist from Stanford University, Dr. David A. Wood, was appointed in 1951. Wood, a stoic, patient man, headed the CRI for 2 decades.

By the third year of operations, the LEO was too busy to get involved in institutional politics. In retrospect, that was one of the troubles I should have made frequent trips back to Bethesda to solidify personal relationships, especially since the leadership (there was changing rapidly, with Dr. Leonard A. Scheele and Dr. Harry Eagle now in top positions and with little back ground or sympathy about our arrangements and goal).

The annual report for 1948-49 proudly proclaimed: "The objective of the Laboratory is clinical research in cancer. With the cancer patient as the local point of interest, the work is oriented along four broad approaches: (1) experimental therapy, including clinical, material for other studies as well as permitting evaluation of such procedures on neoplastic disease; (2) physiology, particularly cardiovascular and respiratory physiology of the cancer patient, and the study of neoplastic tissue, in vitro and in vivo; (3) biochemistry, including metabolic studies on the cancer patient and investigation of such biochemical reactions and; (4) the study of protein fractions of cancer and normal tissue of human origin, utilizing immunochromatography for their identification and differentiation."

This was not wishful thinking. Already 19 publications were printed or in press, and 88 patients had been studied on the ward; this comprised over 3,000 patient-days, explored 10 therapeutic chemicals or procedures, and expanded our pre-LEO experiences. The pathology unit had performed 82 autopsies (18 on our patients) and examinations of 162 biopsy specimens. Even the isotope unit had performed 57 determinations.

The experimental chemotherapy program depended upon clinical observations for the determinations 0 effect (2). Biometric design, random assignment, and double-blinking were features of the future. Our case numbers were insufficient, and the approaches were foreign to our clinical setting. Frankly, we did not miss them at this early phenomenologistood. It did not take much astuteness to recognize that nitrogen mustard and amethopterin were active against leukemias and lymphomas, whereas protopiperin and tibutamide were devoid of useful activity. We were rich in 10 patients and the only effect was severe anaphylactoid reactions (5). Chymotrypsin was not further advocated.

Hydroquinone monohexyl ether, used in depigmentation of rubber, was described to block melanin formation. We obtained a commercial product, purified it, and treated patients having disseminated melanomas. In the animal room, mice with tumors were used to test fungicides, tetrachloro, and esters (2,4-dichlorophenox)acetic acid (2,4-D) for antineoplastic effects.

Studies of the physiology of patients with cancer...

J NATL CANCER INST
In the management of the case, the young patient had previously been treated for cardiovascular disease. However, the development of methods to measure intraarterial and intracardiac blood pressures by means of catheters was leading to observations on the physiology and biochemistry of the tumor.

These measurements, as could be anticipated, were more useful for patients with cardiovascular diseases than for those with neoplastic diseases. They allowed the identification of the nature of the tumor vessels and the demonstration of the tumor-specific antigens. The indicator was the sensitized intestine of the guinea pig, which would be exposed to proteins of normal tissues to ascertain residual reactions to subsequent exposure to tumor proteins. In vivo studies on the physiologic dynamics of leukocytes in man showed the importance of leukocyte removal mechanisms in patients with leukemia and suggested new approaches to leukemia treatment.

The work of Shimkin and others on the physiology of leukocytes in leukemia was leading to observations on the physiology of leukocytes in normal tissues. The approach was to develop methods to measure intraarterial and intracardiac blood pressures by means of catheters, which would allow observations on the increased abnormal vascular supply of tumors in man.

The tumor vessels responded poorly to epinephrine, and the ability to approach visceral tumors, such as metastases to the liver, by the arterial route also enabled the exploration of therapeutic effects of chemicals introduced by the arterial supply. Studies on the physiologic dynamics of leukocytes in man showed that the lung was more active in removing leukocytes than other organs, and that the spleen was less effective in removing them.

In conclusion, the work of Shimkin and others on the physiology of leukocytes in leukemia was leading to observations on the physiology of leukocytes in normal tissues, and the approach was to develop methods to measure intraarterial and intracardiac blood pressures by means of catheters, which would allow observations on the increased abnormal vascular supply of tumors in man.
Dr. Elliott Rapaport demonstrates multilead electrocardiography at a meeting of the American College of Physicians, April 20, 1948. Left to right, foreground: Dr. B. Shacter, Dr. L. Melcher, Dr. E. Rapaport, and Miss M. Brown.

Figure 4—Dr. L. R. Melcher and Mr. R. R. Reed immunize a guinea pig with radioactive antibodies against tissue proteins. The metabolism of this radioactive-labeled material was then studied by determination of the radioactivities in the tissues and excreta of the animal.
SHIMKIN

Infusion of blood between two patients. By means of an arterio-arterial cross connection through polyethylene tubes and with the aid of anticoagulants, up to 150 liters of blood were exchanged between two patients on 12 occasions. Fundamental to the dynamic physiology of blood cells, as well as some clinical therapeutic benefits in patients with marked blood loss, made this technique possible.

An analysis of survival and the effects of some therapeutic factors on survival were of the leukemias (22, 23), lymphomas (24), breast cancer (26). For the leukemias and lymphomas, no increase in survival could be demonstrated over a 30-year period from 1918 to 1948, nor was it related to therapy (27). Earlier reports of cure also indicated that the survival had increased, thus reinforcing the possibility that cure was a palliative for symptoms.

In the early 1950's a mounting debate arose over the classic Halsted radical mastectomy. Proponents, and critics who could elicit no statistic for operative removal beyond simple mastectomy at the University Hospital had a record of their breast cancer material, maintained by a devoted secretary who would eventually die of breast cancer and die therefrom. Life analyses of survival and the effects of therapeutic factors on survival were performed on patients with acute leukemia and that the release form we had devised for admission to the research ward was "psychologically harmful."

The sources of the criticisms were not identified, but we were in the middle of the sticky area of experimentation on human beings.

On a trip to the NCI, I was asked to see the director of the NIH and was accused of experimenting on man. The procedure particularly condemned was hypophysectomy for malignant melanoma (28). We pointed out that the procedure was not being done by us at LEO because none of us would know how to do one, but it was being done by the respected, nationally known neurosurgeon Dr. Howard Naffziger. Moreover, hypophysectomy for advanced neoplasms was also being investigated in Sweden. Whatever may have been the injustices or lack of communication, remedial steps had to be taken. We instituted written protocols for all new departures in our clinical research, which were asked the cancer board of the medical school to review. A symposium arranged with Dr. Otto Guttentag on the subject of human experimentation was held in October 1951, and was well received. An almost visible thawing of attitude was felt by the airing of the problem. We gathered the four presentations for publication but were stopped by the NIH. They, too, were grappling with this sticky problem and formulating their guidelines for the Clinical Center that was being built in Bethesda. In some way, an enunciation from California was considered contrary to possible exchange, with academic freedom that I proceedings final issue of Science papers, in which view and Gutten view, have become subsequent.

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Although I had served a us, we also drew att or sources of interest. Francisco and B out our demise 2150's a mounting debate arose over our procedure of cancer disease with of our procedures.

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Largest one being a pickup truck that was used to accelerate the delivery of supplies from the university warehouses. The process of getting the truck accepted by the Government was ludicrously complex and lengthy. We set up a petty cash fund for the other contributions; from this a television set for the ward was purchased.

I remain convinced that investigations on man should be pursued in absence of financial relationships between the subject and the investigator. Evidence was ample in our experiences to indicate how little reality was contained in the demand for informed consent by the subject, which is now accepted dogma and a stringent requirement. A much more realistic safeguard is the independent doctor-counselor suggested by Guttenberg (29). Even there inadequately encompass children, mentally incompetents, and the trusting and ignorant.

We dealt with people with fatal afflictions predicted to be of rather short duration, for whom standard treatments were ineffective or unavailable. The bravery and fortitude of the patients and their families were constant wonder. Who can forget the brave young wife of a man whose face was being eaten away by a mixed tumor? She nursed him at home and one night he mercifully died, an emaciated Quasimodo without a recognizable face. Who can forget the beautiful children with acute leukemia, in whom remissions were induced with methotrexate or cortisone, and who then would relapse and die before one's eyes? It was always the young father who would collapse, and the mother who would bear up under the tragedy. My advice to such families was to conceive another child, and often the mother was already pregnant.

All the drugs and procedures we had were so limited, so temporary in their effects. Yet despite all cautions, the placebo effect was evident in many of our patients. In anticipation of a miracle, they would eat better, sleep better, require less narcotics, and even gain some weight. Such improvements were ephemeral, and we learned to anticipate them and not to confuse them with therapeutic effects of our drugs.

The patients had to know they had cancer before admission, and almost all of them did. A woman with disseminated breast cancer, however, would ask us not to tell her husband; her husband had just previously asked us not to tell her husband. Cancer was seldom mentioned to the patient. My advice to the patient was to see another child, and often the mother was already pregnant.

The whole staff—physicians, nurses, dieticians, and attendants—was immersed by the activities. After several deaths, in rapid succession, of patients who had become their friends as well, one wanted to send the staff for a vacation to allage their grief. No, it was not a detached, cold experience. It was very warm, human.
experience that could not be communicated to those who had not had such an enrichment in their lives.

The staff was young, but we did have one death. Dr. Nellie Halliday, a biochemist who supervised our clinical laboratory, had chronic ulcerative colitis. Her last few weeks as heartrending as any of the deaths from cancer.

LEO was involved in two major extracurricular activities. I was for 7 years the executive secretary for an all-university cancer research program, which allocated some $300,000 per year for projects on three campuses (32). Bierman continued with the annual national examination of medical and dental students (33), which eventually was found to be the only worthwhile attempt for cancer teaching program of the NCI. The clinical staff participated in various consultative cancer boards at the universities and other hospitals in the area, and resident and research fellows in medicine, pathology, and radiology rotated through our clinical facilities.

One of the original purposes of LEO was to have highly integrated work at the clinical and laboratory level. This aim floundered on so many levels of human activities. Personalities clashed. Clinicians considered the laboratory workers to be available for their projects. The laboratory workers were of a different mind, and to force collaboration was hopeless. Instead, the staff went their separate ways, with collaboration evolving spontaneously between individuals as they found problems of mutual interest. I retain a great amount of skepticism about programs in research based upon collaborative interactions between mature investigators, specialists in programs designed for others by administrative supervisors. Things simply don't work that way. To force the issue results in rebellion, noncompliance, with a staff of compliant technicians rather than independent investigators and sources of original ideas.

**THE CRASH**

The apogee and the nadir of LEO were only a year apart. We continued to report progress in the studies of physiological dynamics of leukocytes in man. Thoracic duct fluid had been analyzed in 10 patients. The effects of sympathetic and parasympathetic drugs on leukocyte dynamics continued to show the importance of the lungs in the sequestration and release of leukocytes into the circulation (34). Additional studies reiterated that leukocytes cells often had a longer life-span than normal leukocytes, the oldest and most mature in leukemia patients. He and Dr. Serafim Masouredis determined the blood flow in human bone marrow by clearance of radioiodine and found it increased in leukemia patients. Bierman et al. (36) performed percutaneous portal vein puncture on 45 patients, measuring glucose and oxygen consumption and blood flow. Portal venograms were obtained by this technique, and a dispute over priorities immediately occurred with the radiology department.

In experimental chemotherapy, 10 chemicals were tried, the most interesting being the new GT-41, discovered by Dr. George Timms of London and eventually to be known as busulfan or Melufan (37). Satisfactory responses were achieved in 16 patients with myelocytic leukemia. The news that we had an interesting new agent for myelocytic leukemia spread rapidly, and a small flood of patients with the disease appeared in internists.

Nitrogen mustard and its analog continued to be the mainstay, along with methotrexate and cortisone. Collidine, 7-azaguanine, Nile blue, the Serratia marcescens polysaccharide, and a soluble methylcholanthrene were tried without therapeutic effect. The University Hospital experience with leukemias, lymphomas, and breast cancer was analyzed. Our comparisons with historical controls, such as acute leukemia in children, demonstrated no significant improvement in survival. We concluded that our therapeutic manipulations, including those with objective effects on tumor mass, were palliative of symptoms and did not alter the neoplastic process and progression.

Laboratory investigations in immunology and biochemistry were also progressing satisfactorily. Meischer and Masouredis prepared radiolabeled antibodies to ovalbumin as a simplified model for extension to more complex proteins. The fate of the antigen and the antibody in guinea pigs was determined, with the conclusion that iodine-labeled antibodies could be used as indicators for the presence or absence of antigenic proteins in vivo (38). The techniques were then applied to virus antibodies, first to enterovirus and finally to the mammary tumor antigen in mice (39). These, in turn, were preliminary to the planned return to human tumors and possible identification of specific antigenic components.

Shaffer, with Dr. Cecil Emtenman (40), studied...
I received official notification that our clinical activities would not be supported after June 30. This decision, the notification stated, was "based on budgetary considerations and should not be interpreted as a reflection on the quality of the work." The director of the CRI offered sympathy; the dean became unavailable; the local press was indignant; but the decision was final. Places for the professional staff were made available at the NCI in Bethesda, each on an individual basis. The research floor that had been added to the new medical school building for the use, and was to be completed some months later, quickly acquired other occupants on the plans.

The last year was a sad one, spent with the remnants of the basement laboratories and the animal room. I returned to my old interests, research on the adenomatous lung tumor in mice, and developed some quantitative studies with Dr. Milton Poliak. Bierman became scientific director of the City of Hope Hospital in Duarte, California, taking Drs. Keith Kellie and Ralph Brown with him. Shack, Shuster, and Dr. Laurens White transferred to Bethesda, but Melcher went into private practice in allergy, and Petrie found a spot on the faculty of the medical school. Brown, our invaluable head nurse, was already at the Clinical Center, and Mense accompanied me East.

Thus after 7 years, Stillwagon, 1.6 million dollars, 550-550-7450 (plus another $5 million for construction we never occupied), and over 130 publications, the LEO was closed. My wife and I were guests at a medical school faculty dinner at which I was presented with a parchment scroll. An admiral came from Bethesda to take charge of the Government property.

The real farewell was on June 4, 1954. The Tint Angel club night club on the Embarcadero, opposite the ship piers of San Francisco, was rented for the occasion. Only the LEO staff was invited and they all came. Alcohol flowed and the atmosphere became heavy with sentiment, loud singing, and a camaraderie described among survivors of sinking ships.

REFERENCES


(20) Shmak MB, Bierman HR, Kelly KH, et al: Triethylseleno-


(36) Bierman HR, Steinbach HL, White LP, et al: Portal hypop-


Pharmacy is ideally situated to develop a sound educational program in this specialty and to do so will require the addition of a qualified staff member of professional rank to develop and administer the program. The area of Pharmacy Administration can also be expanded at the graduate level, but this should present no special problem other than office space for one or more members of the staff. In order to develop this area of instruction, it will be necessary to develop a collaborative program with the School of Business Administration on the Berkeley Campus for such a collaborative program is now in progress.

METROLOGY

Several members of the faculty on the San Francisco Campus have suggested that there is need for the development of a Division of Metrology and if this were agreed upon at some time in the future, the School of Pharmacy at least logical school to develop and nourish the several disciplines involved in physical measurements. This is certainly true unless the School of Pharmacy is expanded into a general campus. The School already offers instruction at the undergraduate and graduate levels in physical measurements which embraces a number of disciplines that would be strengthened by integrating both academic and administrative levels. Mathematics may be regarded as the discipline to Metrology, and there is clearly need for one or more able mathematicians on the San Francisco Campus. Metrology represents an area with special activities as the Optical Spectrographic Laboratory (OPL), X-ray, etc. which is a part of the School of Pharmacy, the Radiology Center, and Development Laboratory. By closer integration of staff members in above areas and by additional staff in the general area of Metrology the program can be properly supported.

In summary, the School of Pharmacy is presently short four offices for research laboratories to house and accommodate the number of faculty required instruction of 80 students in the year. There is need to expand the present to accommodate up to 100 students. There is also need to strengthen and expand instruction in Research Pharmacy and Pharmaceutical Administration. Some additional space will be required for this purpose. Should it be decided that the School of Pharmacy shall develop a Division of Metrology, additional allocation of space will be necessary.

Troy C. Daniels, Dean, School of Pharmacy
course of treatment that fits one of these patients for normal social existence and a productive life. The management of cleft palate patients demands the combined skills of many specialists: plastic surgeons, pediatricians, orthodontists, prosthodontists, radiologists, speech therapists, and others. To help meet the need for this coordinated care, our Cleft Palate Panel was established in 1953 under auspices of the School of Dentistry. It has been supported almost entirely by private funds, and over the years has assisted in the treatment of more than 900 children. In some cases, treatment is undertaken at the Medical Center; in others, the panel provides expert evaluation and recommendations to guide referring physicians and dentists in home communities. Besides rendering a service of inestimable value, this program has made important advances in the evaluation and treatment of cleft palate.

Research in radiology: The AEC-supported Radiological Laboratory now has nearly eight years of experience in the treatment of cancer with the 70-million-volt synchrotron, the world's most powerful x-ray machine. In certain types of patients, this means of therapy achieves results that would be impossible with more conventional treatment, because the extremely high energy of the radiation beam permits the delivery of an effective dose deep in the body with a minimum of damage to intervening healthy tissue. Among tumors that have been treated with the synchrotron are those of the head and neck, uterus, lung, bladder, and thyroid. The Radiological Research Laboratory has made important contributions to x-ray diagnosis. The use of image intensifiers and special television circuits, for example, has made it possible to visualize internal structures exceptionally well while markedly reducing the exposure of patient and staff to radiation; x-ray motion pictures of such complex processes as swallowing and speech require no more radiation exposure than a conventional chest x-ray. The Radioactivity Research Center is recognized as an outstanding laboratory for work with radioactive isotopes. It provides facilities for research programs of many departments, and has made important contributions of its own -- particularly in the study of thyroid function and the evolution of chemical techniques for destroying thyroid tissue in patients with goiter.

Mental retardation programs: When public interest is newly focused on a major medical problem, the feeling that "something must be done" tends to be translated into an assumption: "nothing is being done." There is also a tendency to overlook the prolonged effort required to develop new programs. Actually, the San Francisco Medical Center is doing highly significant work in the field of mental retardation and in the cluster of neurological handicap, sensory disorders and emotional problems from which retardation cannot be segregated. Our Department of Pediatrics has that is recognized by national authorities as an open hub of care for children with cerebral palsy, retardation, and related problems. Working closely with this clinic is the Pediatric Mental Health Unit, which does
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A constellation of occasions and circumstances differentiated into the LEO. After 8 years at the NCI and war service with a parade of acronymic agencies (OSRD, UNRRA, SHAPE, and WHO), I wanted to settle down in an academic environment and contribute to the solution of the cancer problem. Surgeon General Thomas Parran agreed to such an arrangement and even edited an exploratory letter that I drafted to Dr. Francis Scott Smith, dean of the University of California School of Medicine in San Francisco, my alma mater. Dr. Roscoe R. Spencer, director of NCI, was favorable to the concept of colonies and also encouraged me. One of the members of the National Advisory Cancer Council in 1946 was Dr. Robert S. Stone, professor of radiology at the University of California Medical School in San Francisco and a medical director in the Manhattan Project. He heard about me from his academic associates and from my involvement with an extension of the Manhattan Project at the NCI. Dr. Egon Lorenz, who was studying the lifetime effects of low levels of radiation on several species of rodents, was having difficulties with the pathologist assigned to him for the hematology work. I was asked to take over, in the process, I learned some hematology.

One day I was asked to meet Stone. We chatted, and I expounded my ideas on a well-supported combined clinical-laboratory unit on cancer research in an academic environment. I wanted to demonstrate that biomedical research programs of the National Institutes of Health (NIH) could develop as colonies of full partnership with universities and that such research should be pursued by full-time research teams. Stone was interested, and careful. The dean and his cancer committee were in favor, he said, but no money, no space, no academic positions were available.

Despite these discouraging words, an exchange of letters between the president of the University of California and the Surgeon General of the Public Health Service formalized an agreement. A sum of $40,000 was allocated from the budget of the NCI, and negotiations for space were on the way in San Francisco. Dr. Howard R. Bierman, about to leave the Navy, appeared on the scene via an introduction by Spencer. He was a graduate of Washington University in St. Louis and an enthusiastic physiologist who was taking out a patent on a new strain gauge (1). He appeared to be a good man around whom to develop clinical investigations, and a civil service position was obtained for him. He proceeded ahead of me to San Francisco, where I arrived in January 1947. Space for LEO was found at the Laguna Honda Home, a facility for the aged poor of the city's Department of Health. It was a castle housing some 1,500 souls, whose average age was over 85. The name, meaning “deep lake” in Spanish, was derived from its proximities to a water reservoir about 3 miles south of the medical school campus on Parnassus Hill. San Francisco’s director of Public Health, Dr. Jacob Geiger, was an old Public Health Service officer from the plague days in California, a big, pleasant diplomat with a hobby of gathering medals. He, the dean, and the director of the Public Health Service district compiled the necessary documents of agreement, and for the rent of $10 per year we acquired two floors of one wing of the building. The upper floor was to house the clinical beds and facilities; the lower floor was for the

1 Received June 30, 1977; accepted September 3, 1977
2 Supported by Public Health Service contract NIH 251-76-C-0419 from the National Cancer Institute
3 Department of Communis Medicine, School of Medicine, University of California at San Diego, La Jolla, Calif. 92035
basic laboratories, physiology equipment, and animals. Immediately, we ran into long discussions with the administrator of the home, who was not at all sure that rats and mice were included in the agreement. The administrator was a dedicated man with much time on his hands, and discussions with him were interminable.

Contracts were let via the medical school for construction in our area, and reimbursement from the NCI was arranged by one telephone call. Surplus laboratories and office equipment accumulating from demobilization was readily procured, and we were soon sufficiently equipped. By summer we were in place. Surgeon General Parran dropped in to give his blessing.

The basic staff was quickly assembled. Among the earlier additions were a biochemist, Dr. Bernard Shacter; an M.D.-Ph.D. immunologist, Dr. Leo Melcher; and a physicist, Mr. Bruce Shumway. But most important were two indispensable women who really ran the place: Miss Dorothy Wessee, chief administrative assistant; and Miss Marjorie Brown, chief nurse. By the time the facilities were completed in June 1947, 15 people were on the staff.

Meanwhile, Bierman and I were making clinical and academic contact in the area, including seeing a few patients on consultation. One was a man with a disseminated lymphosarcoma, with external nodules covering his whole body. We had ampuls of nitrogen mustard and gave the patient one course. Every nodule disappear ed and the terminal patient sat up and demanded food. News of the miracle, which unfortunately lasted but a short time, spread through the city.

We had meetings with the cancer committee, a consultative cancer board was reorganized, and Bierman was put in charge of the NCI cancer teaching grant to the medical school. With a statistician hired for the purpose, plans were started to devise a national test of cancer knowledge among medical students.

The laboratories reported to the medical school and to the NCI. Good as well as bad consequences came from having more than one bureaucracy to work with. Printing of forms and announcements, for example, was proscribed by Government regulations but simply achieved via the university. Travel to meetings was difficult to finance by the university, but at that time easily arranged with the NCI. Such alternate arrangements were made possible by our several sources of funds. The basic allocation was from the direct operations budget of the NCI; we were, in turn, a "branch" of their structure, loosely placed in the office of the director. The experimental ward was financed by an NCI grant, one of the largest at the time, to the medical school. I expended this money by university rules. A small budget was set up for us by the medical school; this was later derived from the all-university cancer appropriation from the State.

The three sources of funds were reflected in three personnel systems for employment. With the exception of Bierman, members of the scientific professional staff were officers in the Public Health Service. Others on the direct NCI funds were on Federal civil service. The clinical help were hired through the university system. The salaries and emoluments differed and had to be reconciled, a reasonable problem for all but the clinical professionals.

The last item was an Achilles' heel of the activity. I had a fixed idea that clinical investigations should involve no financial arrangements between the patients and the investigators. Thirty years later, I believe this more strongly than ever. The world of the real, even in 1917, however, was out of focus with my beliefs. The medical school faculty derived much of their income from private practice—open or hidden, or rationalized. I soon found that even seeing patients on consultation and not charging for such consultation embarrassed the physician and the patient.

All services were free to patients admitted to the laboratory's ward, and we had no accounting or billing system. Inasmuch as officers of the Public Health Service were "on duty" 24 hours a day, I had control over their activities and allowed no outside practice except for one who supplemented his resources by emergency room attendance on weekends. Such restriction was not applied to civil service employees, whose time after work was their own.

IN FLIGHT

By the end of the first year, the LEO was a fully developed mini-experimental hospital of 15 beds in addition to laboratories for physiologic, biochemical, and immunologic work. The total budget was now $212,000. The staff comprised 9 professional investigators, 12 administrative and technical assistants, 8 nurses, and others for a total of 49 people. Residents in medicine and in pathology were rotated through the facility.

I was secretary of the statewide Cancer Research Coordinating Committee of the University, on the cancer

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board, and chairman of the planning committee for a research floor of the new medical school buildings. Gierman was chairman of the consultative tumor board and of the cancer teaching program for the medical school.

The clinical work was oriented around two internists and required collaboration and participation by many other specialists. Pathology needs were met by setting up a service extension from the medical school, with a full-time technician and resident, thus expanding the Laguna Honda Home pathology services. Radiology needs were initially met by Laguna Honda Home, but required the purchase of a new fluoroscope. For minor surgical procedures, consulting surgeons provided free services; for major surgeons, patients had to be transferred to the University Hospital.

We hoped to develop isotope radiotherapy and assembled the necessary equipment, including a hood with a collecting device on the roof of the building. Three research fellows in radiobiology served with us, but later changed careers to pathology and pediatrics.

The professional staff had clinical appointments at the medical school in experimental oncology, and for administrative purposes they were under the Division of Medicine. We were listed separately in the catalog of the medical school. Our main relation, however, was to the interdepartmental cancer board of the medical school, initially chaired by the professor of pathology, but soon replaced by Stone, the professor of radiology.

He was a capable radiologist and a pioneer of the atomic age (2).

Stone was the emeritus head of the laboratory at the medical school. He enjoyed complete control in his department and voluntary his participation in budgetary and administrative matters of the laboratories. Not having attained this goal, he began to draw up a "constitution" for a Cancer Research Institute (CRI) at the medical school. The rules became increasingly more restrictive and formal, with long hours of acrimonious discussion about specific provisions that seemed trivially detailed.

I finally recognized that the planned institute was being set up for Stone as its director, and that I was seen as a competitor for the position. I announced that my role would continue to remain in the Public Health Service and to head the LEO and that, although the LEO would be within the proposed CRI, I intended to retain control over it whether at Laguna Honda Home or in the new facilities in the medical school. The CRI constitution was soon patched up, and my relations with Stone became formal. The medical school obtained a building grant of $1 million for an extra floor to house the LEO. Stone decided not to become the director, and instead a pathologist from Stanford University, Dr. David A. Wood, was appointed in 1951. Wood, a stolid, patient man, headed the CRI for over 2 decades.

By the third year of operations, the LEO was too busy to get involved in institutional politics. In retrospect, that was one of the troubles: I should have made frequent trips back to Bethesda to solidify personal relationships, especially since the leadership there was changing rapidly, with Dr. Leonard A. Scheel and Dr. Harry Eagle now in top positions and with little background or sympathy about our arrangements and goals.

The annual report for 1949-50 proudly proclaimed: "The objective of the Laboratory is clinical research in cancer. With the cancer patient as the focal point of investigations, the work is oriented along four broad approaches: (1) experimental therapy, providing clinical material for other studies as well as performing evaluation of some procedures on neoplastic disease; (2) physiological, particularly cardiovascular and respiratory physiology of the cancer patient, and the study of neoplastic tissues; (3) biochemistry, including metabolic studies on the cancer patient and investigation of specific biochemical reactions; and (4) the study of protein fractions of cancer and normal tissue of human origin, utilizing immunological techniques for their identification and differentiation."

This was not wishful thinking. Already 19 publications were printed or in press, and 88 patients had been studied on the ward; this comprised over 3,000 patient-days, explored 10 therapeutic chemicals or procedures, and expanded our pre-LEO experiences. The pathology unit had performed 82 autopsies (18 on our patients) and examinations of 102 hospital specimens. Even the isotope unit had performed 57 determinations

The experimental chemotherapy program depended upon clinical observations for the determinations of effect. Biometric design, random assignment, and double-blinding were features of the future. Our case numbers were insufficient, and the approaches were foreign to our clinical setting. Frankly, we did not miss them at this early phenomenologic period.

It did not take much astuteness to recognize that nitrogen mustard and amethopterin were active against leukemias and lymphomas, whereas pyroperen and stilbamidine were devoid of useful activity. We soon found that nitrogen mustard did not have to be spaced over several days but could be given in a single dose, and that the induction of fever did not enhance the therapeutic response (4). Chlorambucil was a local cancer nostrum; we tried it on 10 patients, and the only effect was severe anaphylactoid reactions (3). Chlorambucil was not further advocated.

Hydroxyquinone monobenzyl ether, used in depigmentation of rubber, was described to block melamin formation. We obtained a commercial product, purified it, and treated patients having disseminated melanoma (6). No beneficial effects were noted, and the trial was completed without the subsequent intermediate regulations of "investigational new drug" provisions of the Food and Drug Administration. Therapeutic approaches also included cautious exploration of virus infections; a trend popular at the time and of hypophysectomy for advanced breast cancer and melanoma. In the animal room, mice with tumors were used to test fungicides, terrazoliums, and esters of 2,4-dichlorophenoxacetic acid (2,4-D) for antineoplastic effects.

Studies on the physiology of patients with cancer...
Solved the development of methods to measure intravascular and intracardiac blood pressures by means of strain gauges, and circulation times by means of oximeters. These measurements, as could have been anticipated, were more useful for patients with cardiovascular problems than for those with neoplastic diseases (7). More specific investigations of the fate of transfused leukemia cells indicated the prodigious capacity of the lungs to remove such cells from the circulation. Experience with various intravascular catheterization procedures was leading to observations on the vascularization of tumors and intra-arterial drug therapy.

Biochemical approaches included determinations of serum catecholase (8) and urinary coproporphyrin (9); neither seemed useful indicators in neoplastic disease. As another indication of the need for specificities in neoplastic diseases, blood histamine values in patients with invasive leukemia were of interest (10). The rise in gastric lactic acid after administration of glucose in patients with gastric carcinoma, as investigated by Shafter et al. (11), seemed to demonstrate the anaerobic glycolytic activity of the tumor.

Melcher proceeded with fractionation of tumors and normal tissues for the protein components as the first step toward the demonstration of tumor-specific antigens. The indicator system was to be the sensitized intestine of the guinea pig, which would be exposed to proteins of normal tissues to ascertain residual reaction to subsequent exposure to tumor proteins. In vitro precipitin reactions on antitumor rabbit serum absorbed with a pool of normal organ extracts also were being explored. These attempts to demonstrate tumor antigens received no support from the scientific director of the NCI, who believed that tumors elicit no immunologic response.

AT APOGEE

By mid-1951 the research program of the LEO was in full swing, with the staff and budget at a steady state. Publications numbered 61, with 10 more in press. The clinical group, under Bierman, used increasing use of new sophisticated arteriographic methods that allowed observations on the increased abnormal vascular supply of tumors in man (12, 13). The tumor vessels responded poorly to epinephrine, the ability to approach visceral tumors, such as metastases to the liver, by the arterial route also enabled the exploration of therapeutic effects of chemicals introduced via the arterial supply.

Studies on the physiologic dynamics of leukocites in man (14) showed the importance of leukocyte removal mechanisms in patients with leukemia and suggested that longer survival of leukemia leukocytes was a factor in the disease. Cross-transfusions between patients with leukemia and patients with disseminated neoplasms (15) showed that the lung was more active in removing
enter the circulation through the thoracic duct, this duct was catheterized (16). Regardless of the peripheral lymphocyte or granulocyte count, the lymphocyte count in the thoracic duct lymph remained stubbornly the same. Drainage of lymph fluid up to 10 days did not alter the peripheral lymphocyte count. The resulting information showed that lymphocytes in lymphatic leukemia do not gain access to the blood in increased numbers through the thoracic duct.

Experimental chemotherapy was attempted with about a dozen compounds (17–19). Activity was limited to alkylating agents, antifolic acids, and hormones. Triethylenemelamine was an interesting addition to nitrogen mustard, but less predictable in its effects (20). Cortisone and adrenocorticotropic became available in small amounts and were used in children with acute leukemia. It soon became apparent that, although remissions were induced, their duration was brief and did not add to the survival period (21).

In the absence of formal controls or counteracts, we began in 1948 to analyze historical experiences in the survival of patients with malignant diseases; these experiences were culled from the records maintained by the tumor registry of the University Hospital. The late Dr. Eschholzia Lucia, a trained statistician who was with the registry at that time, not only facilitated the analyses but provided for me an intense postgraduate course in statistics, a topic to which I had not been exposed.
Professor of medicine had a long, friendly chat with surgeons at the L'niversity Hospital in San Francisco and with the use of some of their breast cancer material, main-
contrary to possible policy. Letters and telegrams were exchanged with the dean emerging as a champion of academic freedom. Approval finally arrived, with instructions that I not be identified with the NIH. The proceedings finally appeared in the February 27, 1953, issue of Science 16 months after the meeting (29). The papers, in which I took the research worker's point of view and Guttentag spoke on the physician's point of view, have become classics and have been included in many subsequent compilations on the subject.

DESERT

Although I thought we had met the challenges and had served a useful purpose in confronting the issues, we drew attention as real or possible troublemakers or sources of institutional embarrassment, both in San Francisco and Bethesda. How much this contributed to our demise 2 years later remains unknown, but it certainly must have been an influential factor.

Our work was not free of complications. Our patients, of course, had advanced disseminated neoplastic disease with fatal prognosis, and they were informed of our procedures. There was a 210-pound Texan with mucous fungoides, who looked like a raw steak. By arterial infusions of nitrogen mustard (30), his extremities cleared remarkably. Attempts to clear his face, however, caused development of a hemiplegia, and he lingered for months as a nursing problem. One evening, a terminal patient with lymphosarcoma hit a cigarette in his oxygen tent and sustained fatal burns. But the most dramatic investigations, such as cross-transfusions of blood or drainage of the thoracic duct, everything went smoothly. Neither were we criticized in our attempts to induce virus infections in children with acute leukemia, after we observed a remarkable remission in one little patient who developed chicken pox without our help (31). We eventually admitted almost 500 patients to the experimental ward. These were our main professional concerns and we learned to anticipate them, the initial release form even included agreement to an autopsy. The understanding did not absolve us of negligence nor deprive patients of recourse to legal actions, but it did set the tone and nature of our relationships. In all our 5 years of operations, not a single threat or implied threat of action against us was traced. Two patients did instruct us to terminate our treatment (32).

As much as we had no fiscal arrangements with the patients, we had to guard ourselves against being considered a convenient dumping ground for patients who were terminal in regard to their physical or their financial condition. By insisting upon complete control over our admissions, we avoided the problem quite successfully at the cost of being considered uncooperative by some of our colleagues.

If any patients insisted on making contributions, the largest one being a pickup truck that was used to accelerate the delivery of supplies from the university storerooms. The process of getting the truck accepted by the Government was ludicrously complex and lengthy. We set up a petty cash fund for the other contributions, from which a television set for the ward was purchased.

I remain convinced that investigations on man should be pursued in absence of financial relationships between the subject and the investigator. Evidence was ample in our experiences to indicate how little reality was contained in the demand for complete informed consent by the subject, which is now accepted dogma and a stringent requirement. A much more realistic safeguard is the independent doctor-counselor suggested by Guttentag (29). Even there, the ethical problems do not adequately encompass children, mental incompetents, and the trusting and ignorant.

We dealt with people with fatal afflictions predicted to be of rather short duration, for whom standard treatments were ineffective or unavailable. The bravest and fortitude of the patients and their families were a constant wonder. Who can forget the brave young wife of a man whose face was being eaten away by a mixed tumor? She nursed him at home and one night he mercifully died, an emaciated Quasimodo without a recognizable face. Who can forget the beautiful children with acute leukemia, in whom remissions were induced with methotrexate or cortisone, and who then would relapse and die before one's eyes? It was always the young father who would collapse, and the mother who would bear up under the tragedy. My advice to such families was to conceive another child, and often the mother was already pregnant.

All the drugs and procedures we had were so limited, so temporary in their effects. Yet despite all cautions, the placebo effect was evident in many of our patients. In anticipation of a miracle, they would eat better, sleep better, require less narcotics, and even gain some weight. Such improvements were ephemeral, and we learned to anticipate them and not to confuse them with therapeutic effects of our drugs.

The patients had to know they had cancer before admission, and almost all of them did. A woman with disseminated breast cancer, however, would ask us not to tell her husband; her husband had just previously asked us not to tell her. Cancer was seldom mentioned after that—an unwelcome intrusion known to all but recognized by none.

How important is this contact? The dying woman whose face you stroke and whose hair you rearrange, and the smile that passes between you. The hand of the father of the leukemic child that you grasp and feel its flutter, its sweat, and the almost electrical transmission of his woes to you. We, too, were short.

The whole staff—physicians, nurses, dieticians, and attendants—was immersed by the activities. After several deaths, in rapid succession, of patients who had become their friends as well, one wanted to send the staff for a vacation to assuage their grief. No, it was not a detached, cold experience. It was a very warm, human
experience that could not be communicated to those
who had not had such an enrichment in their lives.

The staff was young, but we did have one death. Dr. Nellie Halliday, a biochemist who supervised our clinical labora-
tories, had chronic ulcerative colitis. Her last few weeks were as heartrending as any of the deaths from
cancer.

LEO was involved in two major extramural activities. I was for 7 years the executive secretary for an all-
university cancer research program, which allocated some $300,000 per year for projects on three campuses
(32). Bierman continued with the annual national ex-
amination of medical and dental students (33), which
eventually was found to be the only evaluative attempt
of the cancer teaching program of the NCI. The clinical
staff participated in various consultative cancer boards
at the university and other hospitals in the area, and
residents and research fellows in medicine, pathology,
and radiology rotated through our clinical facilities.

One of the original purposes of LEO was to have
highly integrated work at the clinical and laboratory
level. This aim floundered on that most human of all
human personality clashes. Clinicians considered the
laboratory workers to be available for their projects.

The laboratory workers were of a different mind, and
force collaboration was hopeless. Instead, the staff
went their separate ways, with collaboration evolving
spontaneously between individuals as they found prob-
lems of mutual interest. I retain a great amount of
sympathy for programs in research based upon
collaborative interactions between mature investigators,
especially in programs designed for others by adminis-
trative supervisors. Things simply don't work that way.

force the issue results in rebellion, noncompliance,
and a staff of complaisant technicians rather than inde-
pendent investigators and researchers of original ideas.

in the same context, the apogee and the nadir of LEO
were only a year apart. We continued to report progress in the studies
of physiologic dynamics of leukocytes in man. Thoracic
fluid had been analyzed in 10 patients. The effect
of sympathetic and parasympathetic drugs on leukocyte
functions continued to show the importance of the
levels in the sequestration and release of leukocytes
into the circulation (34). Additional studies reiterated
that leukemia cells often had a longer life-span than
normal leukocytes. Petrakis (35) measured bone mar-
row temperatures and pressures, which were elevated
in leukemia patients. He and Dr. Serafeim Masouredis
also determined the blood flow in human bone marrow
by clearance of radiolabeled and found it increased in
leukemia patients.

Bierman et al. (36) performed percutaneous portal
vein puncture on 45 patients, measuring glucose and
oxygen consumption and blood flow. Portal venograms
were obtained by this technique, and a dispute over
priorities immediately occurred with the radiology de-
partment.

In experimental chemotherapy, 10 chemicals were
tried, the most interesting being the new GT-41, dis-
covered by Dr. George Timmis of London and eventually
to be known as busulfan or Myleran (37). Satisfactory
responses were achieved in 16 patients with myelocytic
leukemia. The news that we had an interesting new
agent for myelocytic leukemia spread rapidly, and a
small flood of patients with the disease appeared in
referrals.

Nitrogen mustard and its analogs continued to be the
mainstay, along with methotrexate and cortisone. Colchicin,
alloxa.n, azaguanine, Nile blue, the Serratia marcescens
polysaccharide, and a soluble methyliodo-thione were tried without therapeutic effect.

The University Hospital experience with leukemias,
lymphomas, and breast cancer was analyzed. Our com-
parisons with historical controls, such as acute leukemia
in children, demonstrated no significant improvements
in survival. We concluded that our therapeutic manip-
ulations, including those with objective effects on tumor
mass, were palliative of symptoms but did not arrest
the neoplastic process and progression.

Laboratory investigations in immunology and bio-
chemistry were also progressing satisfactorily. Melder
and Masouredis prepared radionuclide-tagged antibod-
ies to ovalbumin as a simplified model for expensive-
more complex proteins. The fate of the antigen and
the antibody in guinea pigs was determined, with the
conclusion that iodine-labeled antibodies could be used
as indicators for the presence or absence of antigenic
proteins in vivo (38). The techniques were then applied
to anti-virus antibodies, first in erythema and lungs
to the mammalian tumor agent in mice (39). These, in
turn, were preliminary to the planned return to human
tumors and possible identification of specific antigen
components.

Shafter, with Dr. Cecil Entenman (40), studied

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plasma sulfhydryl, including its measurement during the growth and regression of a rat lymphosarcoma. Decreases in sulfhydryl levels seemed to reflect increases in sulfhydryl utilization by proliferating tissues.

Dr. Joseph Shack, who was transferred to LEO from the NCI, worked with others (44) on nucleic acids and multiple proteins from calf thymus and mouse lymphoma. Drs. Francis Crick and James Watson announced their resolution of the structure of the DNA molecule in 1953. Postulations in that field were being made by others; the blackboard in Shack's laboratory was filled with odd diagrams of possible structures. Perhaps those could be tested by studies with deuterium. Meanwhile, he was finding some distinct differences in deuteriums extracted from mouse serum and from a mouse lymphoma.

Our isotope unit, under Maserbols, also showed clinical productivity (42), and the material in the pathology unit allowed some reports on unusual metastases (43, 44).

I was unaware of the fact that our fate already was sealed. Visits came from the director of the NCI and from the Surgeon General, both, were taciturn, uncommunicative, and obviously pessimistic. The Clinical Center was about to open, and I was told that 15 beds in San Francisco could in no way be justified when they were concerned about filling 500 research beds in Bethesda. Further concerns about the staffing continued, as much as clinicians were a new addition to NIH and the salaries that could be paid were not competitive. Thus clinicians deployed elsewhere were being pulled back to Bethesda, and Bierman and his associates were among such candidates. Dr. Jesse Steinfield was transferred to NCI to develop isotope studies. He eventually became Surgeon General of the Public Health Service, after two terms at NCI and a period at the University of Southern California.

I was not privy to the high-level discussions about the fate of the LEO that may have taken place at NCI or the university. In April 1953, I received official notification that our clinical activities would not be supported after June 30. This decision, the notification stated, was based on budgetary considerations and should not be interpreted as a reflection on the quality of the work. The director of the CRI offered sympathy, the dean became unavailable; the local press was indifferent; but the decision was final. Places for the professional staff were made available at the NCI in Bethesda, each on an individual basis. The research floor that had been added to the new medical school building for our use, and was to be completed some months later, quickly acquired other occupants on the plans.

The last year was a sad one, spent with the remnants of the laboratory personnel and the animal room. I returned to my old interest, research on the adenomatus lung tumor in mice, and developed some quantitative studies with Dr. Milton Pollard (45). Bierman became scientific director of the City of Hope Hospital in Duarte, California, taking Drs. Keith Kells and Ralph Bron with him. Shack, Shacter, and Dr. Laurens White transferred to Bethesda, but Melcher went into private practice in allergy and Petrik found a spot on the faculty of the medical school. Brown, our invaluable head nurse, was already at the Clinical Center, and she was accompanied by me.

Thus after 7 years, 500 patients, 1.6 million vintage dollars (plus another $1 million for construction we never occupied), and over 130 publications, the LEO was closed (45). Mrs. and I were guests at a medical school faculty dinner at which I was presented a parchment scroll. An administrative officer came from Bethesda to take charge of the Government property.

The real farewell was on June 4, 1954. The Tin Angel night club on the Embarcadero, opposite the ship piers of San Francisco, was rented for the occasion. Only the LEO staff was invited and they all came. Alcohol flowed and the atmosphere became heavy with sentiment, loud singing, and a camaraderie described among survivors of sinking ships.

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The School of Medicine is ideally suited to develop a sound educational program in this specialty and to do so will require the addition of a qualified staff member of professional rank to develop and administer the program. The area of Pharmacy Administration must also be expanded at the graduate level but this should present no special problem other than office space for one or more members of the staff. In order to develop this area of instruction, it will be necessary to develop a collaborative program with the School of Business Administration on the Berkeley Campus. Negotiations for such a collaborative program are now in progress.

METROLOGY

Several members of the faculty on the San Francisco Campus have suggested that there is need for the development of a Division of Metrology and if this could be agreed upon at some time in the future, the School of Pharmacy in its present logical school to develop and nourish the several disciplines involved in this area of physical science. This is certainly true unless the San Francisco Campus is expanded into a general campus. The school already offers instruction at both the undergraduate and graduate levels in physical measurements which embraces a number of disciplines that would be strengthened by integration both at the academic and administrative levels. Mathematics may be regarded as the basic discipline to Metrology, and there is clearly need for one or more able mathematicians on the San Francisco Campus. Metrology represents a broad area of research special activities as the Spectrographic Laboratory (FT, IR, X-ray, etc.) which is a part of the School of Pharmacy, the Radioactivity Center, Research and Development Laboratory. By closer integration of staff members in these areas and additional staff, the general area of Metrology could be properly supported.

In summary, the School of Pharmacy is presently short four offices to house and accommodate the number of faculty for instruction of 80 students in pharmacy. There is need to expand the present office to accommodate up to 100 students in the class. There is also need to strengthen and expand instruction in Pharmacy and Pharmacy Administration of some additional space will be required for this purpose. Should it be decided that the School of Pharmacy should develop a Division of Metrology, some additional allocation of space will be necessary.

Troy C. Daniels,
Dean, School of Pharmacy
Vice President James H. Corley
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source of treatment that fits one of those patients for normal social existence and a productive life. The management of cleft palate patients demands the combined skills of many specialists: plastic surgeons, pediatricians, orthodontists, prosthodontists, radiologists, speech therapists, and others. To help meet this need for coordinated care, our Cleft Palate Panel was established in 1953 under auspices of the School of Dentistry. It has been supported almost entirely by private funds, and over the years has assisted in the treatment of more than 900 children. One cause, treatment is undertaken at the Indian Clinic, in others, the panel provides expert evaluation and recommendations to guide referring physicians and dentists in home communities. Besides rendering a service of inestimable value, this program has resulted in important advances in the evaluation and treatment of cleft palate. The highly successful approach used in the cleft palate program is now serving as a guide to the establishment of a similar referral center for rehabilitation of patients who have been treated for cancers of the face and mouth.

Research in radiology: The AEC-supported Radiological Laboratory saw has nearly eight years of experience in the treatment of cancer with the 70-million-volt synchrotron, the world’s most powerful x-ray machine. In certain types of patients, this means of therapy achieves results that would be impossible with more conventional treatment, because the extremely high energy of the radiation beam permits the delivery of an effective dose deep in the body with a minimum of damage to intervening healthy tissue. Among tumors that have been treated with the synchrotron are those of the head and neck, uterus, lung, and urinary bladder. The Radiological Research Laboratory has made important contributions to x-ray diagnosis. The use of image intensifiers and special television circuits, for example, has made it possible to visualize internal structures exceptionally well while markedly reducing the exposure of patient and staff to radiation; x-ray motion pictures of such complex processes as swallowing and speech require no more radiation exposure than a conventional chest x-ray. The Radioactivity Research Center is recognized as an outstanding laboratory for work with radioactive isotopes. It provides facilities for research programs of many departments, and has made important contributions of its own — particularly in the study of thyroid function and the evolution of chemical techniques for destroying thyroid tissue in patients with goiter.

Mental retardation programs: When public interest is newly focussed on a major medical problem, the feeling that "something must be done" tends to be translated into an assumption: "nothing is being done." There is also a tendency to overlook the prolonged effort required to develop new programs. Actually, the San Francisco Mental Center is doing highly significant work in the field of mental retardation and in the cluster of neurological handicaps, sensory disorders and emotional problems from which retardation cannot be segregated. Our Department of Pediatrics has that is recognized by national authorities as an outstanding clinic for children with cerebral palsy, retardation, and related problems. Working closely with this clinic is the Pediatric Mental Health Unit, which does