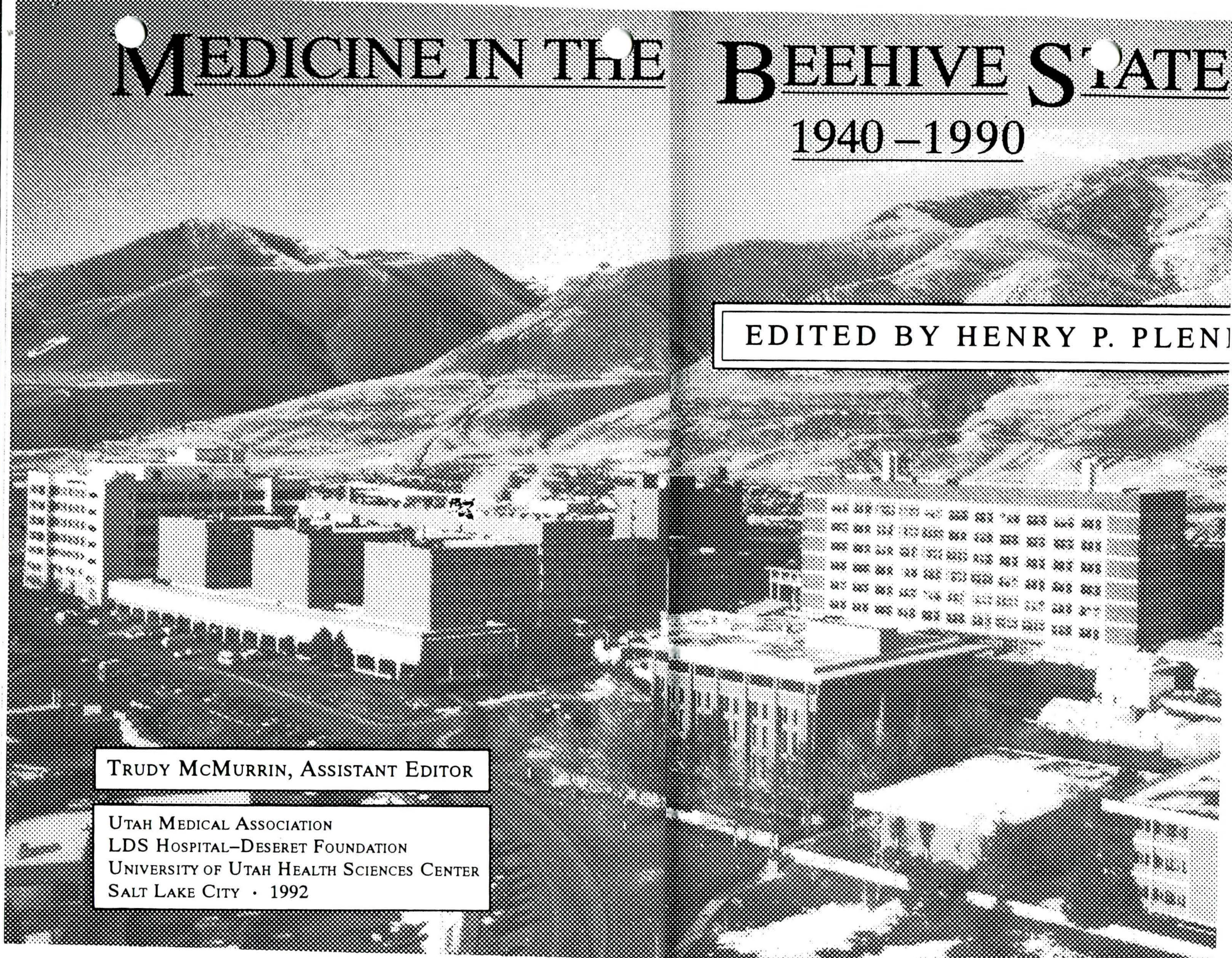

MEDICINE IN THE BEEHIVE STATE
1940–1990

EDITED BY HENRY P. PLEN

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CHAPTER THIRTY-NINE

Medical Informatics: Application of Computers to Medical Science

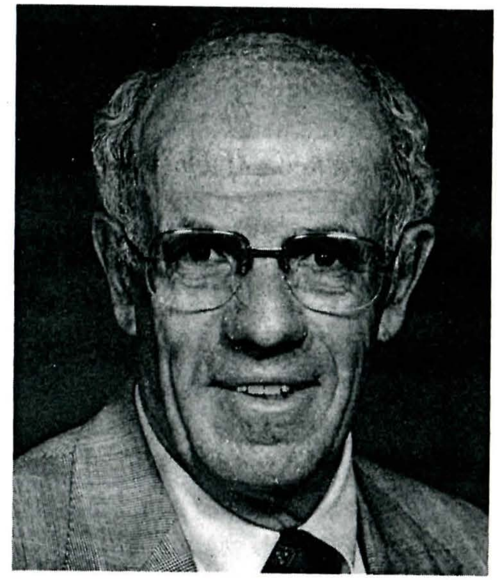
HOMER R. WARNER, MD, PHD

THE DEPARTMENT OF MEDICAL INFORMATICS at the University of Utah originated from the interests and activities of Homer R. Warner. Warner was born in Salt Lake City in 1922. Playing football at the University of Utah was more interesting than his pre-med studies, so he was turned down when he applied for admission to the Medical School. He joined the Navy and was trained as a carrier-based fighter pilot, but the war ended before he saw combat. After the war he completed his bachelor's degree in zoology, applied to medical school again, and this time was accepted.

Warner's class of old veterans, whose average age as medical school freshmen was twenty-seven, graduated on the accelerated war-time program in 1949. Being the only student in his freshman class to answer a difficult midterm question in physiology correctly had given Warner self-confidence and represented an important turning point in his life.

After Warner's graduation, Dr. Max Wintrobe arranged for him to intern at the University of Texas in Dallas with Tinsley Harrison, a very dynamic teacher and role-model, who could make a routine stroke case sound like the most challenging diagnostic problem in the world. Warner's belief that a teacher's principal role is to arouse interest and intellectual curiosity stems from his time with Harrison.

Harrison sent Warner to the University of Minnesota, where he spent the next year as a resident in medicine with Cecil Watson. After



Homer R. Warner.

a year, he continued his residency at the Mayo Clinic in Rochester, where he was stimulated by physiologist Earl Wood to develop a real interest in research.

During these very early days of heart catheterization and diagnostic physiological testing, Mayo Clinic researchers were injecting a blue dye into people, mostly children, with different kinds of right-to-left and left-to-right shunts, trying to detect and quantitate the degree of shunt from the shape of the indicator dilution curve recorded downstream. Warner got so interested in these exciting new developments that he applied for a year in physiology to work with Dr. Wood. Credit for this year was to be applied toward his Board requirements in internal medicine, but he never got back to completing the residency.

Wood got Warner interested in writing and also in developing a method for estimating stroke volume from the shape of aortic pressure waves. He worked out an equation which could be calibrated against the dye dilution or the Fick method and tested it on a series of normal subjects. The stroke volume estimation method performed so well that

Wood suggested the work could become a doctoral dissertation. As a result, Warner returned to the University of Minnesota and spent one more year with Maurice Vissher completing work in mathematics and engineering to fulfill the requirements for a PhD in physiology.

In 1953 Warner returned to the University of Utah to work with Dr. Hans Hecht in the Department of Cardiology at the old Salt Lake General Hospital. He didn't really have a job, but he had applied for a one-year American Heart fellowship, and Hecht was willing to take him since he brought his own support. He helped Hecht set up the catheterization lab using many of the techniques that Mayo had developed. About half way through the year, Dr. Ray Rumel, the only heart surgeon in Salt Lake, and Clarence Wonnacott, the administrator of the LDS Hospital, asked Warner to set up a heart catheterization lab at LDS. In July of 1954 Warner went to the LDS Hospital, where he was to work for the next thirty-two years.

That first laboratory was in a little room on Six West, just outside the doors to surgery. On a budget of $10,000, Warner bought a used fluoroscope and table and the necessary equipment. One end of the room was sealed off and painted black to house the homemade recording equipment. On a table made from a slab door, he mounted a recording camera and a light source on one end and on the other a bank of galvanometers whose mirrors reflected the light back to the recording camera six feet away. The length of the light beam provided the amplification, as electronic amplifiers were not yet sufficiently stable. The electrical signals from the ECG, pressure transducers, and oximeters were fed directly to the galvanometers. At the end of a diagnostic procedure, the twelve-inch-wide role of film was removed from the camera and developed and the wiggly recorded lines analyzed by manual measurement.

At first, most of the cases were patients with congenital heart disease, since surgery for these lesions was new and many accumulated patients were potential candidates for treatment. In June of the second year, 1955, the hospital received a $220,000 grant from the Ford Foundation. The only constraint was that it had to be used for something other than direct hospital operating costs for patient services. Warner convinced Clarence Wonnacott that the grant should be used to set up a research foundation. The first $70,000 built a two-floor animal research facility on the roof, just above the little cath lab, with the animal quarters and Warner's office on top and two new research labs below. The remaining $150,000 represents the endowment for the Deseret Foundation, with the interest used to pay the diener who cared for the animal facilities.

The breakthrough that had attracted enough attention for the grant was a study of the way a pressure wave is distorted as it travels from the root of the aorta out to the periphery, a phenomenon Warner had encountered in his dissertation work. At the time (1955) Warner was taking a class in the mathematics department at the University, and the instructor presented the concept of harmonic or Fourier analysis in which a wave form can be represented as a series of sine waves, each a multiple or harmonic of the first or fundamental frequency. Warner decided to perform such an analysis on a pressure wave recorded from a catheter in the radial artery of a patient. It took most of a day to analyze a single heartbeat using a large slide rule and manual measurements from the pressure recording.

The next day in class the instructor talked about what happens to each of these harmonics as a wave form goes through some system, that is, the transfer function. For example, a radio has a tuner circuit with dials that permit one to adjust the properties of the circuit so that only certain frequencies will be amplified. All the other harmonics will be suppressed. That night Warner did a transfer function analysis of a single heartbeat, looking first at the harmonic content of the upstream pressure wave form, recorded through a catheter up in the root of the aorta, and then at the wave form recorded down at the radial artery. The harmonics of the two wave forms had different amplitudes. The plot looked very similar to the transfer function of the tuned circuit the instructor had used in his illustration.

Warner thought the artery might be distorting the pressure wave by amplifying certain frequencies and decided to build an electrical circuit that could be adjusted until it distorted an electrical wave form the same way the artery was distorting the pressure wave form.

With the help of Dietrich Gehmlich in the electrical engineering department, he built a tunable circuit with a resistor, a capacitor, and an inductor or coil, the properties of each component variable by turning knobs on the front panel. This was Warner's first analog computer. To test his idea, he waited for patients who needed catheters inserted for diagnostic studies. Once he had the catheters in the aorta and radial artery, Warner would leave the patient with his assistant while he ran upstairs to the research lab and quickly adjusted the knobs on the resonant circuit until it was distorting the electrical wave form in the same way the artery was distorting the pressure wave form (i.e., the two output wave forms were superimposed on the dual-beam oscilloscope). Then he could read off the resonant frequency and damping coefficient of the circuit and derive parameters of the artery, such as its elasticity, by analogy.

Warner and Dr. Alan Toronto studied a series of eighty patients using this technique and published the results. As one might expect, the resonant frequency of the aorta gets higher as the vessel begins to lose its elasticity with increasing age. This was the first time that kind of measurement had been made on living patients. Warner applied to the NIH and received funding to purchase the components for a general purpose analog computer for modeling or transfer function studies in other components of the circulatory system. In a few years the department had a whole roomful of these amplifiers that, with wires strung between them, could be used to build circuits to simulate very complex equations that couldn't possibly have been solved without a computer. For the first time, it was possible to describe various phenomena and relationships in a quantitative way.

Warner and his colleagues performed studies using a computer model of the sino-auricular node or pacemaker of the heart. Here, the input to the model was the frequency of nerve firings (action potentials) on the sympathetic and vagus nerves, and the output was the heart rate. Once they were satisfied that their model adequately described the relationship over a wide variety of input variations, they used it to explore the full range of input pattern combinations that might occur clinically.

When the University got its first digital computer, about 1960, Warner decided to study the way the concentration curve following a sudden dye injection is recorded at various points downstream. The transfer function of the upstream and downstream curves becomes a measure of the distribution of transit times of blood particles as they travel between recording sites. For example, transit time through the kidneys is very rapid, something less than ten seconds. However, for blood to flow through the legs and back to the heart may take as long as several minutes. Once again Warner and his coworkers had discovered a very powerful tool. It is useful to know the cardiac output and even more useful to know where the blood pumped by the heart goes.

The researchers were very excited about this work. Since the digital computer in the Merrill Engineering Building was available only after nine o'clock at night, a cot provided a place to rest while the computer ground out solutions to their simulations. Warner got acquainted with Professor Bob Stephenson, who directed the computer center and later became acting dean of the School of Engineering. Together they decided to try to model the diagnostic process using probability theory. Given a certain set of signs and symptoms and the frequency of each finding in patients with any one of a set of diseases, their program could calculate the likelihood that a patient had a particular disease.

To aid the patients coming through Warner's laboratory, they decided to make their model to diagnose thirty-five different forms of congenital heart disease. First, they collected data on how frequently each of fifty different findings, such as murmurs of different kinds and cyanosis, occurred in each disease and how common each disease was in the population of patients referred to the laboratory. After collecting several hundred such cases, a matrix showed the disease on one axis, the findings on the other. At each intersection of the symptom with the disease, a number represented the frequency of that finding in patients with that disease. This table formed the basis for diagnosing patients based on findings recorded by their referring physicians. A comparison of the computer diagnoses and those of the referring physicians showed the computer to be right more often than any of the physicians, based on diagnosis following heart catheterization. The average practitioner, who may see only two or three cases of congenital heart disease in a year, has little experience in diagnosis. These very exciting results were presented at the 1965 meeting of the American Heart Association and published in the *AMA Journal*.

Largely as a result of this groundbreaking study, Warner was successful in getting a grant from the NIH for a digital computer in his own LDS Hospital laboratory. In those days, machines were very expensive. The grant provided about $500,000 per year, and Warner felt a tremendous responsibility to use it productively. He stayed awake nights trying to think of new ways to use the computer to solve significant problems.

Over the next ten years, Warner and his colleagues developed many new computer applications with support from NIH and other sources. After the development phase of a given project (such as automated ECG interpretation) was complete, the hospital administration was asked to begin to charge patients for the service. If the medical staff thought a service was worthwhile, it was offered by the hospital, and in this way the HELP System grew.

The Beginnings of the HELP System

One of the first services Warner and his colleagues automated was the heart catheterization laboratory. They acquired an analog-to-digital converter, probably the first one ever used in a medical setting, and interfaced it to a digital computer. This permitted electrical signals from instruments such as pressure transducers to be fed directly to the computer in digital form. Programs were written which would recognize key features and then carry out whatever analysis was needed to interpret the data. In the cath lab this meant that by the time the physician had finished placing the catheter in the appropriate chambers of the heart and signaled the computer with a wand to make the measurements, he could ask for a display of the results on the oscilloscope, edit the data in any way he wished, and then call for a printout of the final report. This program cut the time for a catheterization and data analysis roughly in half.

Next, many of the group's cath lab programs were moved to the operating rooms. In the early days of open-heart surgery, it was apparent that patients undergoing extensive and prolonged surgery needed careful cardiovascular and respiratory status monitoring. Warner and his associates built programs that allowed the anesthesiologist to record other data, such as intravenous fluid intake, drug administration, and blood gas data, and generate a complete report as the patient left the operating room.

Most of these patients were moved immediately to an intensive care unit (ICU), so it was quite natural that the next phase of this research was designed to continue the monitoring there. The group developed a special console for the ten-bed post–open-heart-surgery unit. The console at the nursing station had a bank of lights — a red, a yellow, and a green light for each patient. The green light indicated that the computer was actively sampling data from a patient. At regular intervals the program would display the data being sampled—a pressure or an ECG waveform. The yellow light indicated that something had happened to that patient's data; that there was an abnormal trend in some variable. Maybe the pressure was dropping or the cardiac output was going down or the peripheral resistance was rising. The computer calculated each of these variables automatically from the shape of the aortic pressure waveform measured through a small arterial catheter introduced by a nurse the night before surgery. The red light indicated an emergency that required immediate action. The yellow and red lights were also interrupt buttons that would make the computer display a graph of the time course of the variable that was out-trending in the wrong direction.

One day Warner went down to visit the ICU and saw a nurse pumping up a blood pressure cuff on the left arm of a patient who had a pressure-monitoring catheter in the right arm. A yellow light showed on the panel. The nurse was embarrassed when she saw him watching her and explained that she didn't know what to do next. They sat down at the computer terminal and looked at all the data in both the computer and the chart. They called the resident and jointly decided that the patient probably was having a cardiac tamponade. The surgeon on call promptly took the patient back to the operating room.

This experience became another important turning point in Warner's approach to the application of computers to medicine. It was clear that just providing data and displaying it in a variety of ways might not be an adequate solution to the decision-making problem. This nurse clearly needed help in interpreting the data, and that interpretation required more data than just the hemodynamic measurements. It required data from other sources, such as the chemistry and hematology labs and x-ray interpretations, but most of all it required that the computer have some medical knowledge. They needed to build intelligence into the system.

Soon afterward, in 1970, Warner went to Europe to give papers at two meetings about ten days apart. In a little hotel overlooking Lake Geneva, he got the idea for computer-based knowledge representation which would provide the basis for the HELP hospital information system. He worked all night between meetings writing the first draft of that program, and by the time he came home, it was ready to try.

The next step was to put some flesh on the skeleton—to put medical knowledge into the shell program that the computer could execute. Two young physicians, Charles Olmstead and Barry Rutherford, were working with Warner, and together they developed a knowledge base of rules and relationships for management of patients in the ICU and for interpretation of measurements made in the cath lab. Their first paper on the HELP system was published in 1972 in *Computer and Biomedical Research*, a journal which Warner has edited for twenty-four years. It is the decision-making capability of the HELP System that distinguishes it from other hospital information systems.

Rutherford was a cardiologist who came to LDS from the Mayo Clinic and later moved to Iowa. Olmstead went on to become a radiation oncologist and moved to Missouri. The HELP System became the primary research effort of the Department of Medical Informatics at Utah, and Alan Pryor, Reed Gardner, and the whole group began working on building an integrated system that would support this kind of decision making. The first version was developed on a Control Data 3200 computer. After eighteen years the researchers could no longer

buy parts for it and had to buy another used machine ("a junker for parts") to keep it going.

A newer machine was needed, but NIH was not interested in funding the second version of something. They finally took the problem to hospital administrator David Wirthlin, who made the decision to support the reprogramming effort and buy the new machine. LDS Hospital now owned the HELP programs. The reprogramming effort took several years because the original version had been written in assembly language for the 3200 machine. After the new system was up and running, the hospital worked out an arrangemen with Control Data Corporation to market it. Income from the com mercialization of the HELP system has provided a very importan source of financial support for the department ever since. (Contro Data sold the system to 3-M in 1987.)

Forming the Department at the University

When Warner first went to LDS Hospital in 1955, he sought ou Horace Davenport and asked for a faculty appointment in the Depar ment of Physiology at the University. As a result of his teachin activities there and his affiliations in the School of Engineering, b 1966 several graduate students were doing doctoral dissertation pro jects under his supervision at LDS. Henry Eyring, dean of the Gra uate School, had invited Warner on several occasions to present h research to Eyring's graduate students in physical chemistry. Aft one such occasion, Eyring suggested that the University establish new department so the students Warner was training could obtain degree which reflected the nature of their training and experience.

Eyring contacted English professor Dr. Jack Adamson, who w then the academic vice president, and he in turn set up a meeting w Warner, Max Williams (dean of engineering), and Franklin Ebau (dean of the Medical School). Adamson asked both deans to explo with their faculties the idea of such a department. A few weeks la Ebaugh reported that the medical faculty felt the time was not ri for such a move, but Dean Williams said the engineering facu would welcome a bioengineering department since there were ma areas of possible joint interest for both research and teaching. So the Department of Biophysics and Bioengineering was established, with laboratories at LDS Hospital and Merrill Engineering.

After about ten years, the department was divided. Bioengineering stayed in the engineering school, and a new Department of Medical Biophysics and Computing was established in the Medical School. Most of the faculty went with Warner into the Medical School, although the department's headquarters remained at LDS until 1985. The Department of Medical Informatics, with fifty-two students, is now the second largest graduate training program in the Medical School for the master's and PhD degrees.

The first graduate of the new program was Stanford Topham, an electrical engineer whose dissertation was a study of the control of cardiac output during exercise which significantly changed the way such clinical problems as the treatment of acute myocardial infarction are viewed today.

The Department Faculty

Alan Pryor came to the University in the mid-sixties with a background in mathematics and computer experience at NASA. For his doctoral dissertation he produced a program for the automated interpretation of the electrocardiogram that was used by the LDS Hospital until 1985, when it was replaced by a commercial system.

Getting automated ECG interpretation accepted by the cardiologists at the hospital was a real challenge. They could always find fault with it until Pryor got top electrocardiographer Alan Lindsay involved enough that Lindsay felt it was at least in part *his* program. Then Lindsay went to his colleagues in cardiology, showed them the facts, and convinced them that the program was doing a more consistent job of interpreting the electrocardiograms than they were. The department learned that to get this new technology accepted by users they must first convince someone respected in the field and then let that person sell it to his or her colleagues.

Pryor has been the architect of many of the underlying computer science aspects of the HELP System and has worked to achieve the

goals originally set for the system and to make it a commercially viable product that can be used by other hospitals.

Reed Gardner's background was electrical engineering. He took responsibility for the hardware, and, in those early days of digital computers, expanded the ways for getting data in and out of the computer by designing systems for displaying information graphically and improving methods for interfacing analog equipment to digital computers for the operating room and ICU. He is prominent in the American Thoracic Society as the leader of the computer group.

Astrophysicist Paul Clayton was using television methods to observe and track the motion of the border of the sun that resembled very closely the methods Warner and his group were using to track the border of the left ventricle. Clayton had no initial background in physiology or medicine, but became knowledgeable in those fields by working closely with Dr. Hal Liddle, developing some special databases that allowed Liddle to track his patients closely. The fine papers produced from Clayton and Liddle's collaboration have had an impact on the direction the field of cardiology has taken. With Phil Frederick and the radiology department, Clayton developed the first automated radiology system. He is now head of the informatics unit at Columbia University and operates a multi-million-dollar IAIMS program there.

John Morgan, who had a degree in electrical engineering from BYU, developed a system for automatically coding diseases using the record room computer. He joined the faculty for a few years after graduation, then quit to develop a minicomputer-based version of the system he had created for LDS Hospital. In less than three years of selling his system to hospitals around the country from the back of a motor home, Morgan built a company which he sold to 3-M for $16 million. In appreciation, he gave the department a $100,000 grant which now supports the John Morgan Fellowship.

Justin Clark came to the department in the mid-sixties with a background in physics. After graduating, he joined the faculty and began working at Primary Children's Hospital on computer-based instrumentation for measuring physiological variables, particularly respiratory and cardiovascular parameters in newborns. Clark is a true

Drs. Homer R. Warner, Alan Pryor, and Reed Gardner with Control Data 3300 at LDS Hospital, about 1975.

inventor, and some of his patents are very remunerative for PCMC.

Mark Skolnick's arrival added a completely new dimension to the department's work. His computer applications in genetic epidemiology and genome mapping are discussed in his chapter elsewhere in this volume. The work of Skolnick and his group has brought the department international attention and has generated a new medical informatics subspecialty.

Peter Haug had received both his medical training and computer experience at the University of Wisconsin. After his residency at Utah, he stayed to become a member of the faculty. His areas of interest are natural language processing and decision support. Haug has worked with Warner on the decision-support algorithms for the Iliad project, and he is responsible for the latest version of the radiology component of the HELP System, replacing Paul Clayton.

Stan Huff, a Utah-trained pathologist, joined the medical informatics faculty in 1985. He has become a leader in the field of patient

medical records and database design, and his concepts are being incorporated in the National Library of Medicine's massive Unified Medical Language project.

Dennis Parker, a medical informatics PhD, went to the radiology department of the University of California at San Francisco, where he developed one of the first high-speed CT devices for medical imaging of moving organs like the heart. He returned to the medical informatics faculty six years ago and has been pursuing his interest in spatial reconstruction of images and pattern recognition.

The Move to the University

In 1985 the University Hospital signed a contract for the HELP System with Control Data Corporation. Chase Peterson, vice president for health sciences, wrote Warner a letter, saying "We are installing your system. What are you going to do about it?" In a meeting it was decided that Warner rather than one of the younger faculty should move to the Medical School, since they perceived the task of getting HELP running at the University Hospital as integrally linked to the long-range future of the department and involving primarily political challenges. So Warner gave up his research career award and moved into space on the "A" level of the Medical School, across from the laundry.

The dean provided funds for a small TANDEM computer capable of running the HELP programs and intended for developing new applications tailored to the needs of the hospital and clinical staff. But Warner was not given access to the HELP System at the University because the "pure vanilla" version provided by Control Data was not allowed to be changed at all, and none of its clinical or decision–making features had been implemented as of this writing in mid-1991.

Frustrated by this situation, Warner responded to a need expressed by Dr. William Odell, chair of the Department of Medicine, for a program to supplement the learning experience of third-year medical students during their clerkship on the medical wards. Over the next few years, an expert system program was developed for the Macintosh computer with the help of experts from the Department of Internal Medicine representing nine different subspecialties. With support from a National Library of Medicine grant, a knowledge base was constructed representing more than 500 diseases which is currently being used by all medical students at Utah. The program, called Iliad, is marketed by Applied Informatics under contract from the University and is now used by more than thirty other medical schools.

Iliad has three modes of operation. It can act as a consultant on real cases by providing a differential diagnosis and suggestions and explanations at each stage of the work on a patient. In a second mode, Iliad can generate a simulated case of any disease in its knowledge base, allow a student to ask for findings (history, physical exam, laboratory, x-ray, etc.), and require the student to propose working hypotheses (diagnoses) based on what he or she knows at each stage of the workup. Students at Utah are required to work up simulations each week in both this learning mode and the test (Iliad's third) mode and are evaluated on their performance. It has been clearly demonstrated that students do improve their diagnostic proficiency by using Iliad, but that improvement is content specific.

It has been convincingly shown that one doesn't become a good generic problem solver: one becomes a good problem solver in a given area through experience in solving problems in that area. In other words, an expert cardiologist is not necessarily an expert hematologist. In the Iliad project, doctors have run the simulations to see how they do. They "muddle through" in areas where they are not experts, but in their own areas they focus quickly and get to the vital data in the most cost-efficient way. Iliad is designed to teach students in the same way. Rather than simply providing a list of findings to be memorized for a disease, Iliad organizes them into "clusters" or patho-physiological entities, and these entities are then formed into higher-level diagnostic entities. The students can take advantage of the patho-physiology Iliad has taught them to solve problems in clinical medicine.

The University is searching for Warner's successor as chair of medical informatics at Utah. The evolution of this new discipline over the last three decades has been exciting, with Utah playing a prominent role. Utah may lead the way in the next decade as well, since the necessary people, institutions, and attitudes are already well established.