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ACM Conference on the

History of Medical Informatics

acm



November 5 — 6, 1987
National Library of Medicine
Bethesda, Maryland

CONFERENCE PROGRAM

8:50 - 9:00	Welcome	9:00 - 10:30	Clinical Data Processing
9:00 - 10:30	Keynote Addresses Donald A. B. Lindberg, M.D. Joshua Lederberg, Ph.D.		Cesar A. Caceres, M.D. Thomas L. Lincoln, M.D. Hubert V. Pipberger, M.D. (Discussant)
11:00 - 12:30	Planting the Seeds - A Panel Wilfred J. Dixon, Ph.D. Robert S. Ledley, D.D.S. Harold Schoolman, M.D. Eugene A. Stead, M.D. Bruce D. Waxman, Ph.D. William S. Yamamoto, M.D. (Moderator)	11:00 - 12:30	Health Care Information Systems Morris F. Collen, M.D. Charles D. Flagle, Dr. Eng. Carlos Vallbona, M.D. (Discussant)
	Lunch		Lunch
1:30 - 3:00	Computing Systems G. Octo Barnett, M.D. Wesley A. Clark, Ph.D. Charles E. Molnar, Sc.D. Thelma Estrin, Ph.D. (Discussant)	1:30 - 3:00	Patient Management Systems Homer Warner, Ph.D., M.D. Melville H. Hodge William E. Hammond, Ph.D. (Discussant)
3:30 - 5:00	Signal and Image Processing Gwilym S. Lodwick, M.D. Jerome R. Cox, Jr., D.Sc. Judith M. S. Prewitt, Ph.D. (Discussant)	3:30 - 5:00	Clinical Decision Making Lee B. Lusted, M.D. Jack D. Myers, M.D. Casimir A. Kulikowski, Ph.D. (Discussant)
	Banquet		Lawrence L. Weed, M.D.

The banquet will be held at the Holiday Inn, 8120 Wisconsin Avenue. There will be a reception from 6:30 to 7:30.

Exhibits and demonstrations of various NLM projects and services will be on display in the Lobby of the Lister Hill Center during coffee breaks and the lunch period on both days of the conference. The Learning Center will also be open to visitors during those times.

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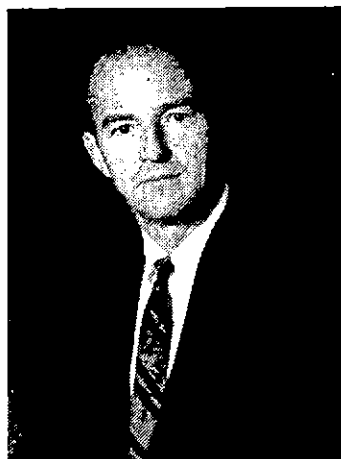
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SPECIAL ADDRESSES



Donald A. B. Lindberg, M.D. is Director, National Library of Medicine. He received an A.B. degree from Amherst College in 1954 and an M.D. degree from Columbia University in 1958. Prior to joining NLM in 1984, he was affiliated with the University of Missouri-Columbia where his responsibilities included Professor and Chairman, Department of Information Science, School of Library and Information Science (1969-71), Director, Information Science Group, School of Medicine (1971-84), and Professor of Pathology, School of Medicine (1969-84). He has written or coedited four books, was the chief editor of four proceedings, is on the editorial board of three journals, and is the managing editor of the Springer-Verlag Lecture Notes in Medical Informatics series. His honors include Distinguished Practitioner in Medicine (NAPM, 1983) and the Silver Core Award (IFIP, 1986).

Joshua Lederberg, Ph.D. is president of The Rockefeller University (since 1978). He received his B.A. degree from Columbia College in 1944, entered medical school, and then took a leave of absence to do research with Dr. Edward L. Tatum at Yale University. While at Yale, where he received his Ph.D. in 1947, he discovered the mechanism of genetic recombination in bacteria. From 1947 to 1959 he was professor of genetics at the University of Wisconsin. In 1958, at the age of 33, Dr. Lederberg was corecipient of the Nobel Prize in Physiology or Medicine for his work in bacterial genetics. He joined the faculty of Stanford University School of Medicine in 1959 and served as chairman of the Department of Genetics until coming to The Rockefeller University in 1978. While at Stanford he also held the titles of professor of biology and professor of computer science. He has received numerous awards, has worked on many government advisory committees, and serves on the boards of a variety of institutions.



Lawrence L. Weed, M.D. is Professor of Medicine Emeritus, University of Vermont (Professor of Medicine 1969-84). He currently works full time as President, PKC Corporation, a small software company that markets microcomputer-based medical software aids to clinical decision-making (the Problem-Knowledge Coupler). He received a B.A. degree from Hamilton College in 1943 and an M.D. degree from Columbia University in 1947. From 1961 to 1969 he was on the faculty of Case Western Reserve University. He joined the University of Vermont in 1969 as Professor of Medicine, Professor of Community Medicine (until 1979) and Director of PROMIS Laboratory (until 1981).

PLANTING THE SEEDS



Wilfred J. Dixon, Ph.D. is President, BMDP Statistical Software, Inc. Until his retirement in 1986, he also was Professor of Biomathematics (since 1967), Biostatistics (since 1955) and Psychiatry (since 1973), University of California, Los Angeles. He received a B.A. degree from Oregon State College in 1938, an M.A. degree from the University of Wisconsin in 1939, and a Ph.D. degree from Princeton in 1944. He has held offices in the Institute of Mathematical Statistics, the American Statistical Association and Biometric Society, and the International Statistical Institute. He is Associate Editor of *Biometrics* and *Annals of Mathematical Statistics*.



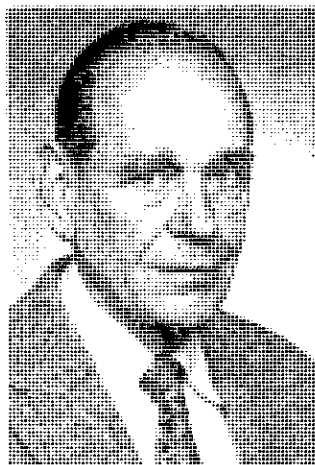
Robert S. Ledley, D.D.S. is Director of Medical Computing and Biophysics Division (since 1975), Professor, Department of Radiology (since 1974), and Professor, Department of Physiology and Biophysics (since 1970), Georgetown University Medical Center. He received a D.D.S. degree from New York University in 1948 and an M.A. degree from Columbia University in 1949. He has written, edited or coauthored eight books and has been awarded numerous patents. He is the Editor-in-Chief of four journals including *Computers in Biology and Medicine*.



Harold Schoolman, M.D. is Deputy Director for Research and Education, National Library of Medicine (since 1977) and Clinical Professor, Georgetown University (since 1970). He received the M.D. degree from the University of Illinois in 1950. He joined the faculty of the Cook County Graduate School of Medicine in 1954 and became affiliated with the Veterans Administration Hospital – Hines, Illinois in 1962. He moved to Washington to become Director, Education Service, Central Office, Veterans Administration in 1967 and joined the National Library of Medicine in 1971. His honors include the NIH Director's Award (1983).

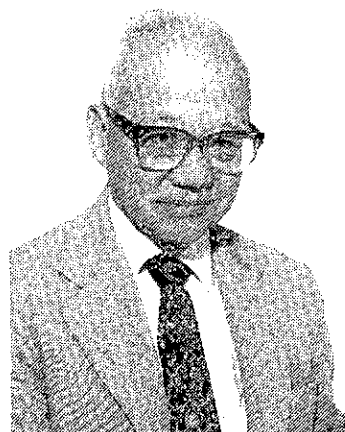
PLANTING THE SEEDS

(CONTINUED)



Eugene A. Stead, Jr., M.D. is Florence McAlister Professor Emeritus of Medicine, Duke University (since 1967). He received the B.S. and M.D. degrees from Emory University in 1928 and 1932. After faculty appointments at Harvard, he became a professor of medicine (1942-46) and dean (1945-46) of the Emory University School of Medicine. In 1947 he joined Duke University as Florence McAlister Professor of Medicine and Chairman, Department of Medicine. He has been an officer in several professional organizations and an editor of three journals. His numerous awards include the Distinguished Teacher Award, ACP (1969), Abraham Flexner Award for Distinguished Service to Medical Education, AAMC (1970), and the Kober Medal, AAP (1980).

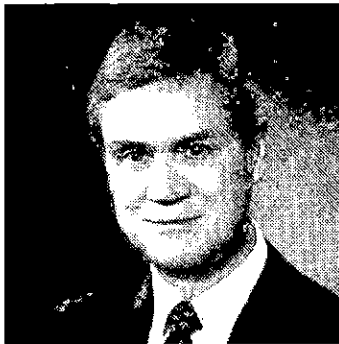
Bruce D. Waxman, Ph.D. is the Acting Chief of the Development Integration Division, Research and Engineering Directorate, Defense Mapping Agency. He received a B.A. degree from the University of Pennsylvania in 1952, an M.A. degree from the University of Connecticut in 1955, and a Ph.D. degree from the University of Chicago in 1973. He was the Executive Secretary, Advisory Committee on Computers in Research, NIH (1961-65), the Chief of the Special Research Resources Branch, NIH (1965-68), Director, Health Care Technology Division, NCHSR (1968-73), and a Senior Research Scientist at NCHSR until 1983.



William S. Yamamoto, M.D. is Professor and Chairman, Department of Computer Medicine, George Washington University (since 1983). He received an A.B. degree from Park College in 1945 and an M.D. degree from the University of Pennsylvania in 1949. He joined the faculty of the University of Pennsylvania in 1950 and moved to George Washington University to become Professor and Chairman, Department of Clinical Engineering (1971-83). He is on the editorial board of three journals including the *IEEE Transactions on Biomedical Engineering* and *Computers in Biomedical Research*.

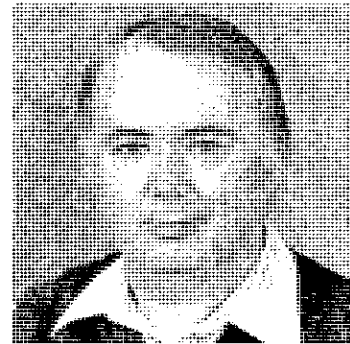
COMPUTING SYSTEMS

G. Octo Barnett, M.D. is Professor of Medicine at the Harvard Medical School and also at the Harvard-MIT Division of Health Sciences and Technology, MIT (both since 1980). He has served as Director, Laboratory of Computer Science, Massachusetts General Hospital, since 1963. He received a B.A. degree from Vanderbilt University in 1952 and an M.D. degree from Harvard Medical School in 1956. He is on the editorial board of seven journals including *Computers in Biomedical Research*, *Computers in Biology and Medicine*, *Computer Methods and Programs in Biomedicine*, and *Methods of Information in Medicine*.



Wesley A. Clark is a senior consultant to academic, governmental and industrial organizations (since 1972). He co-founded the consulting group of Clark, Rockoff and Associates in 1984 and has acted as Visiting Professor of Computer Design at Washington University since 1986. He received an A.B. degree from the University of California, Berkeley in 1947 and joined the MIT Whirlwind Computer Project in 1952. In 1964 he was appointed Research Professor of Computer Science at Washington University and later directed the Computer Systems Laboratory (1967-72). He received the ACM-IEEE Eckert-Mauchly Award for Computer Architecture and is a charter recipient of the Computer Pioneer Award of the IEEE.

Charles E. Molnar, Sc.D. is Professor and Director, Institute for Biomedical Computing, School of Medicine (since 1983) and Director, Computer Systems Laboratory (since 1972), Washington University. He also holds the appointment of professor in the Departments of Computer Science, Electrical Engineering, and Physiology. He received B.S. and M.S. degrees from Rutgers University in 1956 and 1958 and an Sc.D. from the Massachusetts Institute of Technology in 1966. In 1985 he was granted the Javits Neuroscience Investigator Award in recognition of his contributions in the neurologic and communicative sciences.



Thelma Estrin, Ph.D. is Assistant Dean for Continuing Education, School of Engineering and Applied Science and Director, Extension Division of Engineering and Science, UCLA. She received the B.S., M.S., and Ph.D. degrees from the University of Wisconsin in 1948, 1949, and 1951. In 1961 she became a major participant in launching the Data Processing Laboratory at the UCLA Brain Research Institute and served as director of the laboratory from 1970 to 1980. She served as President, IEEE Engineering in Medicine and Biology Society and was elected a fellow of the IEEE and AAAS in recognition of her contributions to the application of computers to biomedicine.

SIGNAL AND IMAGE PROCESSING



Gwilym S. Lodwick, M.D. is Professor Emeritus, Department of Radiology, University of Missouri School of Medicine and Visiting Professor, Department of Radiology, Harvard Medical School (both since 1983). He received the B.S. and M.D. degrees from the University of Iowa in 1939 and 1943. He has been affiliated with the University of Missouri since 1956 and has had appointments in both radiology and bioengineering. He received the Gold Medal for Outstanding Contributions to Radiology, XIII International Congress of Radiology (1973) and is on the editorial board of seven journals, including *CRC Reviews in Medical Informatics* and *Journal of Medical Systems*.

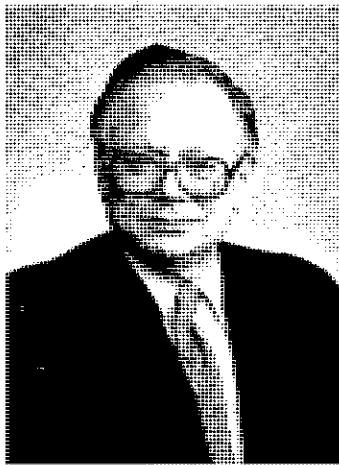
Jerome R. Cox, Jr., Sc.D. is Chairman and Professor, Department of Computer Science, Washington University (since 1975). He also holds the appointments of Associate, Division of Health Care Research (since 1973). He received the S.B., S.M., and Sc.D. degrees in electrical engineering from the Massachusetts Institute of Technology in 1947, 1949, and 1954. After graduation he joined the faculty of Washington University. He is a past Chairman, DCRT Review Committee (1983-84) and has been an associate editor or on the editorial board of five journals, including *Computers and Biomedical Research* and *IEEE Transactions on Biomedical Engineering*.



Judith M.S. Pruitt, Ph.D. is president of MEDIMATICS and Intelligence, Inc., consulting companies that provide services in systems design, strategic planning and technology risk management for medical informatics and telematics applications. She received a B.A. degree from Swarthmore College in 1957, an M.A. degree from the University of Pennsylvania in 1959, and a Ph.D. degree from Uppsala University in 1978. Her career spans academia, industry and government service. From 1971 through 1983 she was in the Office of the Director, DCRT, NIH. She then spent a year as Stoker Visiting Professor, Ohio University, and joined AT&T Bell Laboratories with responsibilities for the company's new medical ventures (1984-1986). She is on the editorial board of several journals and has held numerous posts in the IEEE organization.

CLINICAL DATA PROCESSING

Cesar A. Caseres, M.D. has maintained a private medical practice in internal medicine and cardiology since 1971. He also is the president of a consulting firm and directs the non-profit Institute for Technology in Health Care. He received his B.S. and M.D. degrees from Georgetown University in 1949 and 1953. He joined the faculty of George Washington University in 1960 and later organized and served as Chairman of the country's first Department of "Clinical Engineering" (1969-71). He has published nine books with others in preparation. Several have been the first texts in their respective fields.



Thomas L. Lincoln, M.D. is Senior Scientist, Systems Sciences Department, The RAND Corporation (since 1967). He also is Professor, Research Pathology (since 1987), and Chief, Clinical Information Systems (since 1977), at the Los Angeles County/University of Southern California Medical Center. He received a B.S. degree in zoology in 1955 and an M.D. degree in 1960; both degrees were from Yale University. His areas of research include medical information systems, medical system requirements, curriculum development and biomedical modeling. He also serves as the medical editor for *Software in Healthcare*.

Hubert V. Pipberger, M.D. is Professor Emeritus of Clinical Engineering and of Medicine, George Washington University (since 1982). He received a B.A. degree in 1938 and an M.D. degree from Rheinische Friedrich Wilhelms University in 1951. He joined the faculty of Georgetown University in 1956 and came to George Washington University in 1971 as Professor of Clinical Engineering and of Medicine. Among his honors are the IFIP Award of Distinction (1979) and the AHA Cardiologist of the Year (1981). He currently serves on the editorial board of four journals including *Computers and Biomedical Research* and *Methods of Information in Medicine*.



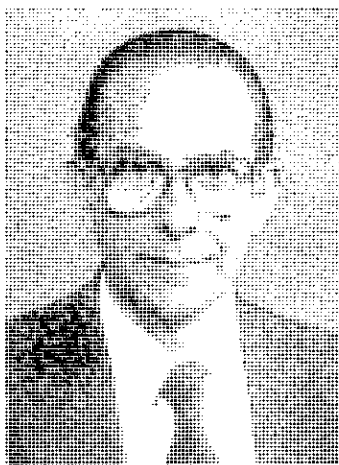
HEALTH CARE INFORMATION SYSTEMS



Morris F. Collen, M.D. is Consultant, Division of Research, Kaiser Permanente Medical Care (since 1983). He received B.E.E., M.B. and M.D. degrees from the University of Minnesota in 1934, 1938 and 1939. He joined the Kaiser Foundation Hospitals as Chief, Medical Services, Oakland in 1942. He later served as Director, Medical Methods Research, Kaiser Research Institute (1968-1979) and Director, Division of Technology Assessment, Permanente Medical Group (1979-1983). He is the author of four books and is on the editorial board of four journals. In 1987 he became a Scholar-in-Residence, National Library of Medicine to continue his study of the history of medical informatics.



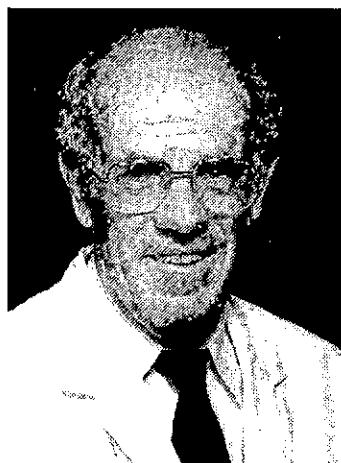
Charles D. Flagle, D.Eng. is Professor Emeritus, Department of Health Policy and Management (Professor 1963-1984) and Senior Research Associate, Health Services Research and Development Center, The Johns Hopkins University. He received the B.E., M.Sc. and D.Eng., degrees from The Johns Hopkins University in 1940, 1954 and 1955. His honors include the Kimball Medal of the Operations Research Society of America (1984). He is on the editorial board of *Methods of Information in Medicine* and *Health Systems Research*.



Carlos Vallbona, M.D. is Professor and Chairman of Community Medicine (since 1969), Professor of Rehabilitation (since 1967), and Professor of Family Medicine (since 1981), Baylor College of Medicine. He attended the Universidad de Barcelona where he received B.A. and B.S. degrees in 1944 and an M.D. degree in 1950. He joined the Baylor faculty in 1956 and four times has been elected to the Outstanding Faculty by a graduating class. He is on the editorial board of seven journals including *Methods of Information in Medicine* and *Informatics and Medicine*.

PATIENT MANAGEMENT SYSTEMS

Melville H. Hodge has a consulting practice and is a member of the Board of Directors of TDS Healthcare Systems Corporation. He received a B.S. degree from Northwestern University in 1952 and was a Sloan Fellow at the Stanford University Graduate School of Business (1960-61). He was with the Lockheed Missiles and Space Company from 1955 to 1971. In 1971 he joined Technicon Data Systems where he later served as President and Chief Executive officer (1973 to 1977). His present consulting activities build upon his experiences in early stage, technology-oriented companies as well as his understanding of the sophisticated management techniques used by the larger corporations.



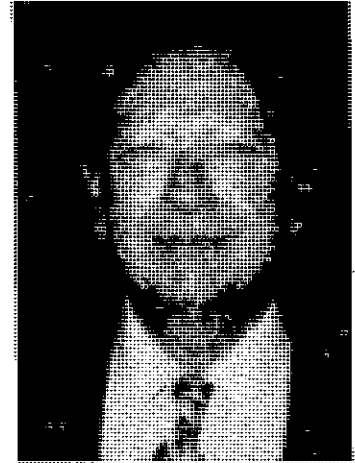
Homer R. Warner, M.D., Ph.D. is Professor and Department Chairman, Department of Medical Informatics (formerly Medical Biophysics and Computing), and Research Professor of Surgery, Department of Surgery, University of Utah (since 1973 and 1966). He received B.A. and M.D. degrees from the University of Utah in 1946 and 1949 and a Ph.D. degree from the University of Minnesota in 1953. He is the editor of *Computers and Biomedical Research*, and is the Principal Investigator for the Utah IAIMS Development Project.

William Ed Hammond, Ph.D. is Professor of Community and Family Medicine, Professor of Biomedical Engineering and Head, Division of Medical Informatics, Duke University. He received the B.S.E.E. degrees from Duke University in 1957 and 1967. He has served as the program chair for two AAMSI Congresses and is on the editorial board of *Computers and Biomedical Medicine* and *CRC Critical Reviews in Medical Informatics*.



CLINICAL DECISION MAKING

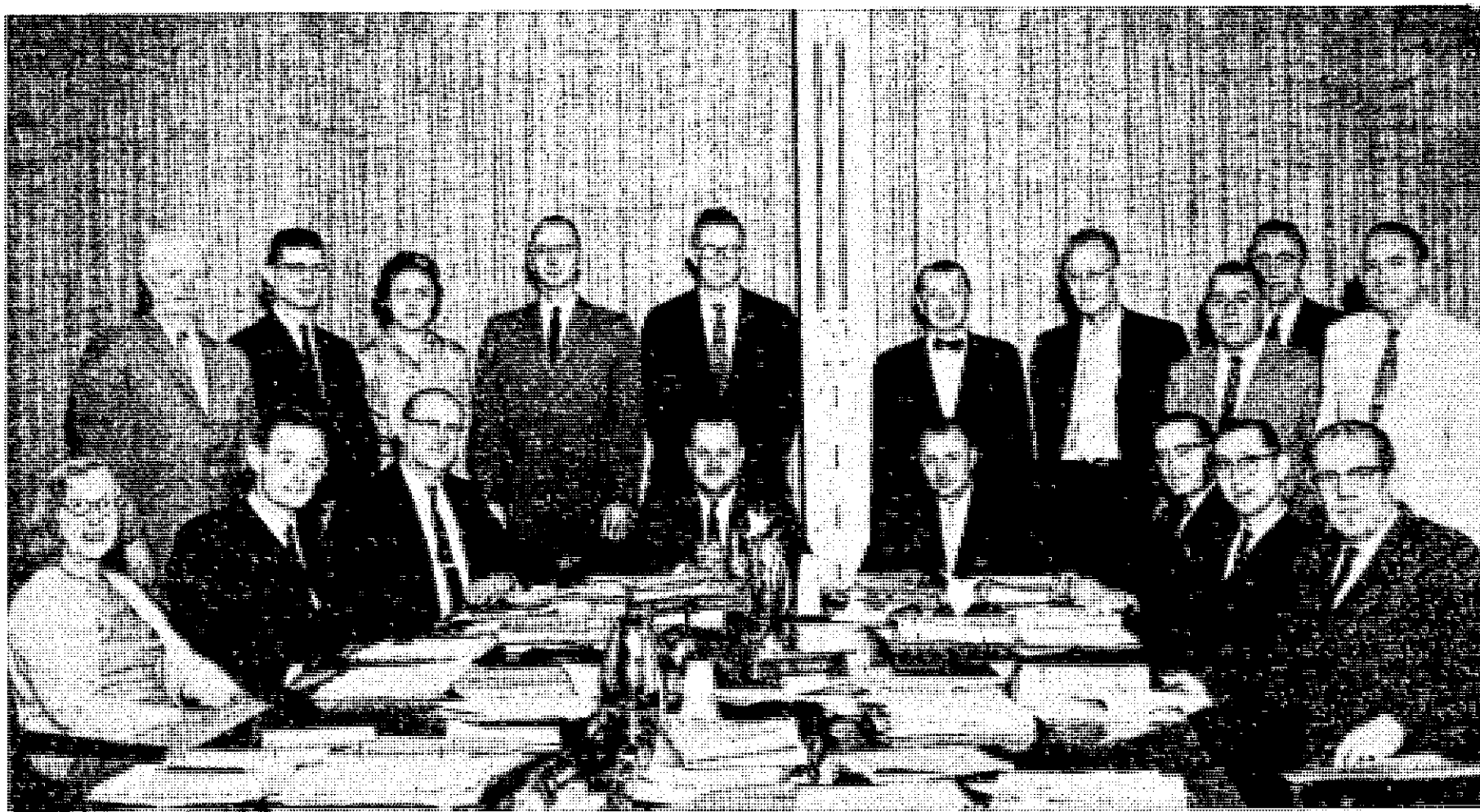
Lee B. Lusted, M.D. is Clinical Professor, Department of Radiology, University of California, San Diego and Adjunct Distinguished Member, Department of Academic Affairs and Department of Radiology, Scripps Clinic and Research Foundation (both since 1978). He received a B.A. degree from Cornell College in 1943 and an M.D. degree from Harvard Medical School in 1950. From 1969 to 1978 he was Professor of Radiology and Vice Chairman, Department of Radiology, The University of Chicago. He was a co-organizer of the Society for Medical Decision Making in 1979 and was the founder and Editor-in-Chief of *Medical Decision Making* from 1979 to 1985.



Jack D. Myers, M.D. is University Professor Emeritus (Medicine) Retired at the University of Pittsburgh (since 1985). He received the A.B. and M.D. degrees from Stanford University in 1933 and 1937. He was on the faculty at Duke University and came to the University of Pittsburgh in 1955 as Professor of Medicine and Chairman, Department of Medicine; in 1970 he was appointed University Professor (Medicine). He is a past president of the Association of Professors of Medicine (1963-64) and past Chairman of the National Board of Medical Examiners (1971-75). His honors include the Robert H. Williams Award, APM (1974), the Alfred Stengle Memorial award, ACP (1979), and the Distinguished Teacher Award, ACP (1981). He has been a Visiting Professor of Medicine at over 35 universities.

Casimir A. Kulikowski, Ph.D. is Professor and Chairman, Computer Science Department, and Director, Laboratory of Computer Science Research, Rutgers University. He received B.E. and M.S. degrees from Yale University in 1965 and 1966, and a Ph.D. degree from the University of Hawaii in 1970. He has organized several workshops on Artificial Intelligence in Medicine and is the Principal Investigator of the Rutgers Research Resource on Artificial Intelligence in Medicine. He is the co-author of a book on building expert systems.





NIH ADVISORY COMMITTEE ON COMPUTERS IN RESEARCH – MAY 1962

Seated Left to Right: Mary A. B. Brazier, W. Ross Adey, Otto Schmitt, Ralph W. Stacy, Joseph E. Schenthal, William N. Papian, James M. Sakoda and Homer R. Warner.

Standing Left to Right: Fay M. Hemphill, George S. Malindzak, Jr., Rose S. Doying, George A. Sacher, Jr., Max A. Woodbury, Lee B. Lusted, Alston S. Householder, Bruce D. Waxman, Scott Adams and David Garfinkel.

INFORMATION SHEET

History of Medical Informatics Conference

Demonstrations

On both days of the Conference, various demonstrations are scheduled during coffee breaks and over the lunch hour.

The following projects of the Lister Hill National Center for Biomedical Communications will be demonstrated in the lobby of the Lister Hill Center:

1. Electronic Document Storage and Retrieval System
2. AI/Rheum
3. Information Retrieval Experiment.

Grateful Med, a microcomputer-based software package which provides a user-friendly interface to selected NLM databases, will be demonstrated in the Visitor's Center in the lobby.

The Learning Center (B1 level, one floor below the auditorium), where visitors can investigate and use new educational technologies in the health sciences, will also be open during coffee breaks and over the lunch hour.

Special Demonstration: There will be a demonstration of the Problem-Knowledge Coupler by Dr. Lawrence L. Weed in the Lister Hill Auditorium from 5:15 to 6:00 p.m. on Thursday, November 5.

Coffee Breaks and Meals

Coffee will be served during breaks in the area behind the Visitor's Center in the Lister Hill lobby.

Box lunches will be provided for all registrants on both days of the conference. Lunches may be picked up in the Lister Hill lobby after the end of the morning session. Participants may take their lunches to one of two rooms on the B1 level of the building (one floor below the auditorium): the classroom and room B1N-30Q (across from the classroom). Lunches may also be taken into the cafeteria, also on the B1 level. Weather permitting, some participants may also wish to take their lunches to the terrace outside of the Lister Hill lobby.

Please note that no food or beverages are allowed in the Lister Hill Auditorium.

The banquet on November 5 will be held at the Bethesda Holiday Inn, 8120 Wisconsin Avenue, a short walk from the Library. The reception begins at 6:30 p.m. and the dinner at 7:30 p.m.

ACM Conference on the

History of Medical Informatics



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Conference Proceedings

**Papers Presented at the Conference
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**Sponsored by the
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Special Interest Group on Biomedical Computing**

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The Association for Computing Machinery
11 West 42nd Street
New York, New York 10036

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Conference Chair

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Charles Babbage Institute for the History of Information Processing

INTRODUCTION

It is fitting that this proceedings on the history of Medical Informatics should begin with an historical introduction. As many are aware, ACM initiated the series with the history of personal workstations in 1986. I first heard of the series at the 1986 ACM Annual Conference and told Adele Goldberg that I thought a history conference on Medical Informatics would be useful. She followed that up, found some others with an interest, and an ad hoc Program Committee was organized.

In parallel with this, I contacted Karen Duncan and she expressed enthusiasm about the idea. She suggested that the Special Interest Group on Biomedical Computing (SIGBIO) might become the conference sponsor. During the week of MEDINFO-86 I met with the SIGBIO Board and they agreed to sponsor the meeting. We also held some preliminary Program Committee meetings and established the scope and structure of the conference.

We felt that a history conference on medical informatics would be of general interest for three reasons. First, the field is young enough so that most of the pioneers are in good health, and can share their insights. Second, perhaps more than any other application area, Medical Informatics has made great contributions to computer science; we believe that there are lessons to be learned from this interaction between theory and application. Finally, a review of our current perceptions in the context of the early goals of Medical Informatics should provide insight into how our objectives are changing with the computer technology.

We decided that participation in the program would be by invitation. Because the field of Medical Informatics is so broad, we elected to concentrate on clinically oriented contributions between 1950 and 1975 in the United States. Even with this constraint, the Program Committee found the selection process difficult. There were so many major contributions! Finally we put together a program that everyone was pleased with; nevertheless, each committee member still had at least one more name he wished to add.

The previous pages have identified the people who organized this meeting and the names of the participants who shared their experiences and thoughts. The constraints of time and geography limited our discussions, but the conference could not have been put together without everyone's effort and cooperation.

These individual efforts were complemented by the assistance of several organizations. First, I wish to express my appreciation to SIGBIO for sponsorship; without their support the conference would not have come into being. Also I thank the following cooperating organizations for their help: the American College of Medical Informatics, the American Association for the Advancement of Science, and the Charles Babbage Institute for the History of Information Processing.

Two supporting organizations also contributed greatly to this conference. The National Library of Medicine provided the facilities, performed the audio and video recording and managed the registration process. They also assisted John Parascandola, the Local Arrangements Chair, in his many, many assignments. The Johns Hopkins University Applied Physics Laboratory provided clerical, publication and general support for the conference; they also managed to get all my letters out on time.

Finally, I must thank those who are reading these words. What would a conference be without attendees? More importantly, how can we learn from the past if we don't understand it? Speaking personally, I have enjoyed reading these proceedings and helping with the conference. Thanks to everyone who made it come about.

Bruce I. Blum
Laurel, MD

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Professor Peter L. Reichertz
1930 - 1987

Although this conference is limited to the history of medical informatics in the United States between 1950 and 1975, there are few in this field who have not been influenced by the work of Prof. Dr. med. P. L. Reichertz

IN PRAISE OF COMPUTING

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I shall describe briefly some early work in applying computing systems to clinical laboratory, diagnosis, and medical records problems. If we compare the early work with what can be done now, we shall see many examples of enormous improvements in speed and power of computing techniques. A particularly striking difference in comparing 1960 with 1987 is the very much more widespread use of computing devices now and the shift in the pattern of scientific and business work to depend upon automated information systems for support of ordinary professional functions. In other words, computing systems really work now, and lots of people really use them.

Let me first establish this contrast and share with you the pleasure this day brings to all of us in taking pride in these accomplishments. We should do this first, because I shall end by drawing attention to some desirable changes that have not occurred over the 25 years. The organizer of this conference, Bruce Blum, urged us to include personal remembrances, so I shall do so.

My own interest in computing arose grudgingly from two requirements, one scientific and one professional. I was working under NIH support on an infectious disease problem when I moved from Columbia Presbyterian to the University of Missouri in 1960, taking my NIH grant with me. This in itself may add an element of nostalgia, since most institutions no longer permit residents to hold grants and NIH can barely fund one-third of the applications from senior faculty nowadays. In any event, my interest turned to a systematic investigation of the (then and now) poor correlation between in vitro and in vivo antibiotic sensitivity of bacteria that infect lung and blood. I did not believe (and still do not believe) that 24-hour disc-diffusion growth inhibition was a reasonable measure of the bacteria's susceptibility to antibiotic killing or growth inhibition. I reasoned that the battle between bacteria and

pulmonary macrophages was probably over in 20 minutes to an hour. Hence I wanted to study bacteria growing in liquid media, with and without antibiotics. To do this I built a machine, along with a sophomore undergraduate physics student.¹

The observations the machine permitted gave a great deal of insight into this problem, although never the ultimate secret.² Nevertheless we were able to prescribe therapy based on these experiments that unquestioningly cured patients with subacute bacterial endocarditis and other infectious diseases on whom others had given up. In any event, computers were necessary to process and organize the output data, and to model the processes of bacterial growth. The progression of steps we took in developing our data processing was rather pitiable in modern terms. First we learned how to wire nixie tubes to display the numbers that represented optical measurements of light scatter (hence bacterial growth) in the hundred or so test tubes that cycled past the light source. In the next version of the machine we took these signals to a Victor adding machine printer. We pasted up the tapes in rows, then read down the resulting columns to sum growth over an individual tube. Next we output the whole run to paper tape which we read into a Burroughs 205 computer. This was the beginning of wisdom, but the Burroughs was not a nice computer and paper tape was awkward. Our next step was to re-design the machine to output to a card punch so that we could process on the "modern" IBM 1620 computer. In both cases, the computers resided in "open shop" mode in the basement of the University Mathematics Department. The Computer Center Director was a half-time job held by an assistant professor of mathematics who was never given tenure. We usually processed at midnight because there would be no one to object if we vacuumed out the detritus from the tape reader.

All this was quite good fun with one exception: namely, I was simultaneously supposed to be directing and supervising clinical chemistry, clinical microbiology, a section of the sophomore path class, and doing frozen sections. The biggest practical problem was getting correct reports out of the clinical laboratories and to the clinics and wards. The blackest day I can remember was when I was called to deal with the potential problem that Clinical Chemistry might not get out any of today's reports before they

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reached quitting time. Even blacker was the discovery that they also hadn't reported the previous day's AutoAnalyzer runs.

My personal love was Microbiology. This was a well run laboratory that always got the work out. Unfortunately the report slips--which pathologists in those days personally signed--usually contained a great and imaginative assortment of spellings of the bacteriological names. This may not have actually impeded patient care, since the clinical house staff receiving them also did not spell with much precision. It did, however, allow the Professor of Microbiology to hold me and the Pathology Department up to ridicule and contumely. This academic paragon did not, of course, know that the Record Room had at all times hundreds of lab reports on which the patient names did not even match the patient unit numbers. These were not permitted to be placed in the charts, and hence were lost forever. Misspelling was only one of our problems.

I made a number of managerial changes to put a temporary "fix" on the reporting problem. The next morning was the brightest day I can remember; it suddenly occurred to me that the computing system I was using for the antibiotic sensitivity experiments could be used to solve my clinical laboratory problem as well. After all, I reasoned, computer programs always spelled things the same way day after day, and the tabulating printer certainly was faster than the folks running the laboratory typewriters. In addition, I could establish limits, so that at least some of the ridiculous errors could never again be reported out and truly life-threatening findings could be identified for telephone reporting. Once one yielded to this line of thinking, it immediately became obvious that the product of the clinical labs (with the exception of the Blood Bank) was purely information: hundreds of thousands of items per year. Tables outside the programs could contain editing and limits values, pointers to other medical record elements, pricing and quality control data, etc.

That day was my moment "on the road to Damascus." I had been seriously troubled by my divided loyalties between pushing ahead in the research laboratory, while simultaneously knowing the clinical laboratory needed attention. I would then spend futile hours correcting spelling and dilutions in the clinical labs while feeling neglectful of the research. That day I realized computers were the answer to the common problem in both settings: namely, information control. From that moment forward I have been professionally happy, and committed to working out the best uses of automated information systems.

The first electronic laboratory reporting system at Missouri (and I believe the first anywhere) was--as you can easily imagine--a kludge too.^{3,4} We could not do much better, since we did not even have a computer in the Medical School. I arranged a system of pre-punched cards, in which each card contained a line of the ultimate lab report. These were arranged in a kind of pigeon roost from which the lab secretaries composed the messages. Using punch cards on the wards on which

to write the clinical order to accompany the specimen worked out well, and various envelopes kept things together during the specimen processing. Incidentally, I was astounded a few years later to see that Warner Slack at the University of Wisconsin had devised an almost identical pigeon roost to hold the cards that provided the basis for his patient history system.

Getting our laboratory results printed on the wards was a problem, since there were no teleprocessing systems even if we had owned a computer. We solved this by converting the cards to paper tape, and using the paper tape to drive circuit codes into what Teletype Corporation called a "Stunt Box." This in turn activated the print circuits to teletype Model 28 printers which we installed in linen closets at the ward and clinic locations. The whole business was slow--and incredibly noisy--but it worked. We summarized the decks of cards--at midnight as usual--in the IBM 1620. This reduced each report to an individual punched card with massive use of "over punches" into the x and y fields. Most of the resultant cards had so many illegal codes that they looked like lace doilies. An easy by-product of all this was a billing punched card for each transaction. These were interpreted and sent to the Business Office. I took considerable glee in knowing that no one in the Business Office, nor in their auditors Price, Waterhouse, had the slightest idea what to do with punched cards. Actually they read them and entered the numbers into posting machines.

The only down-side effect of the new lab system was a deal I made to finance the operation. Since we were printing directly to the patient locations, I discharged 20 pretty co-eds who had been employed to deliver lab reports. That was the first but not the last time I heard colleagues say I was "destroying life as we knew it."

This old original laboratory reporting system did of course get replaced. We brought in an IBM 1410 for the Medical School and implemented what amounted to a fast turnaround batch system using punched card input and output. The memory on the 1410 was 40,000 characters; our languages were Autocoder, Fortran, and COBOL.

In this system the input was written to a patient record as well as a batch print file. Consequently patient unit numbers really had to be correct. We added Modulus Eleven self-check digits to all patient numbers, persuaded the Record Room to rearrange the filing system, and persuaded the hospital administrator that all his Addressograph-Multigraph plate-stamping equipment really needed replacing in any case. Self-check digits were also used for lab reports and specimen numbers. I imagine Missouri was first here too. I have never been able to understand how American hospitals got along without self-check digits, since European hospitals use them with an even better algorithm.

The 1410 system was implemented in the laboratories with a new kind of input terminal: what became the IBM 1092 Densely Coded Matrix.

This was a joint development between IBM and the University of Missouri. Its original purpose was to enter size, shape, color, and cutting instructions for the garment trade in New York, but it seemed to me ideal for lab reporting. One used plastic overlays to redefine the key designations and microswitches to detect unique notches on the individual overlays.

The matrix keyboard got me my NIH automation grant. We had a terrific proposal to use the 1410 to do complete lab automation integrated into hospital patient record keeping. The obvious missing piece was some kind of device to input the data. Since the new IBM matrix device--indeed the whole 1050 system--was unpatented and unannounced, I could not include these descriptions in the grant proposal. I knew this would draw a site visit. At that time Melvin Belli had just pulled off his trial scene trick of leaving the leg-shaped package wrapped in butcher paper on the courtroom desk. I took a leaf from his book and draped the sheet metal prototype of our reporting device with an Operating Room sheet at the head of the Dean's Conference Room. Essentially we were daring the site visitors to ask us to breach our confidentiality agreement. It worked. They stared, but they never asked. And they approved the grant request.

The 1410 system worked quite well but was replaced in time by a true on-line system once the 360/50 became available. The latter got to be a rather extensive system, including a lot of quality control, cost analysis, interpretation, etc.⁵ I know some of those programs ran for fully 20 years.

In the course of this work the University of Missouri formed the Medical Computer Program, and I became its first director beginning in 1962. The commitment of the School to make a serious investigation of computers was made by the Dean, Vernon Wilson. He encouraged us to test the question, "Could computers contribute something to teaching, practice, and research in medicine?", and he did this with much encouragement, advice and support. He was a really fine academic leader. I saw the task to be to create an institutionally-based information utility, to establish a multidisciplinary group including medical, engineering, and mathematical skills, and to support and encourage creative ventures in the professional services of the School and the Hospital. Gwili Lodwick in Radiology at Missouri was certainly at the head of this list. It also included computer groups in Pathology, Dietary, the Dean's Office, and subsequently Surgery, then Medicine and Pediatrics. I still believe central information groups should be institutionally-based, preferably as academic departments of their own; certainly not as service units within other departments.

Incidentally computer science has not been mentioned so far because there was none. I remember vividly some years hence getting a telephone call from the Vice President for Academic Affairs at the University. He asked, "Is there such a thing as computer science? Someone wants to make a new department." Our group had spent a lot

of time convincing the Personnel people to believe in job descriptions and career ladders for computer programmers, system analysts, system programmers, technical writers, etc., so this was not so much of a leap of faith for us as for the Graduate School.

Other events must be mentioned briefly. Use at Missouri of the AMA Current Medical Terminology tapes in the Consider system was really fun. We used sets of symptoms and findings from patient cases as search arguments against the AMA structured text that constituted fairly regularized disease definitions. This produced a differential diagnosis: at least diagnoses to "consider."⁶ The latter were of course ranked according to disease prevalence at the University of Missouri Medical Center as reflected in its discharge diagnosis file. These searches were first done in batch mode. It was clear, however, that teaching of students and residents would be greatly enhanced if we could go on-line. We did this using the IBM 1410 at a time when IBM had not yet produced even its first cathode ray tube terminal. Our display was a Control Data Corp. CRT kludged onto the 1301 RAMAC disk controller. To his credit, the IBM field engineer showed us how to hook it up so the controller thought it had a second RAMAC unit. This CMT work has been subsequently extended by Scott Blois and his Reconsider collaborators, who have added many improvements in software services. To our mutual regret, AMA has not made comparable improvements to the data base itself.

I should mention, however, that even the early version of CMT (later called CMIT) contained literature references. These were part of the tape record, even though they were not part of the printed books. This impressed upon me the tremendous power of the formal scientific literature, as well as the great scope of even the central core of medical knowledge. We frequently demonstrated the system with half a dozen excellent clinicians present, in addition to students and residents. I'm certain there never was a time when the differential diagnoses Consider produced did not far exceed the range of thinking and knowledge of the observers. Our simple reasoning that "you can't diagnose something you don't consider" was compelling then and remains so today.

The Regional Medical Program must be mentioned. To me, this was a wonderful development by the Federal Government. It turned out to be short-lived, but during this period we had the privilege of testing the Caceres PHS system for EKG interpretation. Luther Terry was PHS Surgeon General at the time. He called to initiate the demonstration and trial. This was the first time the Caceres system had been used "in real life" outside the Federal labs. Now that I am a "Fed," I can understand better why this was so. We tested it statewide in 22 different kinds of settings. We found it to be the most appealing and understandable of all the RMP-proffered aids to medical care. I should also note that in addition to Dr. Caceres, Hubert Pipburger from the Veterans Administration was most generous in

giving me help and advice in this RMP project. I won't describe the Caceres system in detail; I hope he will do this. The bottom line scientifically is that it worked extremely well. In general practice settings, 90% of the tracings were normal; 70% from a group of three cardiologists were normal; and 50% from tertiary care hospitals were normal. Fortunately "normal wave form" was a highly reliable statement, as were many of the 150 interpretations. The statements concerning complex arrhythmias were hampered by the relatively short length of tracing then being studied. The bottom line from the point of view of health services research was that the system, with its costly data acquisition carts, transmission, and processing charges was relatively expensive for a rural area like central Missouri but an instant economic success in cities like St. Louis and San Francisco.⁸

A turning point for me professionally came in 1971 after about ten years of directing the Medical Computer Program. We had by then fully operational information systems in clinical laboratory, radiology, dietary, business office, and an institutional integrated file that combined all these medical data with discharge diagnoses, surgical operating room records, surgical pathology and cytology diagnoses, and EKG interpretations. The Clinical literature system was lagging. We had established an SDI system for scientific journal articles and were prepared to leave the rest to NLM! I realized at the time that the future of the field and my own desires lay in research and teaching, not with hospital service systems. The Computer Program had grown from five persons and \$98,000/year in 1962 to 125 people and over \$4 million in 1970. Consequently we recruited Dr. Peter Reichertz to become director of the Computer Program, and I formed the Information Science Group. The latter has ever since been dedicated to efforts to train the cadre of scientists and health professionals that are needed to build the theoretical and scientific basis for future advances in this field.

This brings me to closing on the topic, what has not happened in 25 years? Briefly, we have not seen the creation of the body of theory and principles that should underly our efforts. That we use better, faster computers and more pleasant display devices is simply due to our coupling with the aerospace and business technology evolution. More importantly, medical informatics has remained reasonably well coupled with advances in understanding of basic biomedical fields. This is a struggle: "how to keep current in a technical area and in clinical medicine simultaneously." We can already see that the cutting edge research in molecular biology/ biotechnology is seriously challenging even the best people in medical informatics to make room once again for brand new ideas. Biotechnology is especially challenging because at the moment it benefits so much from mathematical computation at a time when medical informatics has half-way convinced itself it needs only symbolic reasoning.

The real value of a day of retrospection such as this one must surely be to see more clearly how

to progress. The day is just starting, so we must not draw hasty conclusions. Yet I'll bet we will see and hear lots of reasons today to invest in individual creative investigators, that we will see many examples of the need for an atmosphere of interdisciplinary research on topics of fundamental importance, and that we will end the day wanting scope and support for building the formal academic basis for medical informatics.

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How DENDRAL was conceived and born.
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As agreed with your organizers, this will be a somewhat personal history. They have given me permission to recall how I came to work with Ed Feigenbaum on DENDRAL, an exemplar of expert systems and of modelling problem-solving behavior. My recollections are based on a modest effort of historiography, but not a definitive survey of and search for all relevant documents. On the other hand, they will give more of the flow of ideas and events as they happened than is customary in published papers in scientific journals -- accounts so dry that Medawar lugubriously calls them fraudulent {43}; cf. Merton & Zuckerman {44, 45, 61}. These authors point out that the standard scientific publication is narrowmindedly devoted to the context of justification. The DENDRAL effort (along with much of medical informatics) is dedicated to discovery: should we use a different standard for its history?

I hope it will be eventually possible to divert my colleagues from the more important work they do from day to day, and join me in a larger effort at historical research and informed consensus. My account is inevitably incomplete, especially about what others were thinking at a given moment. Built into the phenomenon of history, as soon as enough time has passed to enable some detached judgment, the evidence becomes frail, and we become vulnerable to the myths we create. Understanding all of these limitations, I will no longer qualify every remark: it should be implicit that each is "to the best of my recollection / or/ as best as can be inferred from the fragmentary documentary record".

I will assume you are generally familiar with DENDRAL, and will concentrate mainly on material not found in the published papers, especially as there is a comprehensive synopsis {41}.

As computer science is not my primary profession, my relationship to it has been more episodic; and I can more readily isolate how I came to take some part in it, at Stanford from 1962 - 1978, mainly in very close collaboration with Ed Feigenbaum, Bruce Buchanan, and a host of others. My central scientific commitments have been to molecular genetics, starting when I was a 20-year old medical student in 1945 {38}. At Columbia and then at Yale, I worked on the genetics of bacteria, a specialty which converged with the role of DNA as genetic information. My first academic appointment was at the University of Wisconsin from 1947 - 1958; then I went to Stanford in 1959 to take part in the reconstruction of its School of Medicine (formerly in San Francisco) at the Palo Alto campus. My role was to found a new Department of Genetics; I had no plan to be working with computers. In fact, I met Ed Feigenbaum in 1963. Then, promptly after he moved from Berkeley to Stanford faculty in early 1965, we initiated the collaboration that became the DENDRAL project.

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These were hardly random events: I go back a few years to pick up the relevant premonitory strands.

Figure 1
Conceptual and Experiential Threads
Leading to the Dendral Project [JL view]

- 1) 1937-43. Leibniz dream
Logic & Axiomatic Method -- studies in Columbia College
- 2) 1941, 53, 62. Computer hardware: desultory exposures.
- 3) 1947 ff. Information-theoretic formulations in genetics
- 4) 1953 ff. Introspections about the history of bacterial genetics.
- 5) 1960. Instrumentation development for Mars exploration: NASA
- 6) 1955, 59, 61, 63. Meet Minsky, Djerassi, McCarthy, Feigenbaum

(In every biographic-historic account in science, one seeks an interplay of personality, ideas, institutional setting, and other externalities.)

- 1) Starting in grade school, I had fantasies that echo Leibniz' dream (see {13}) of a "universal calculus" for the "alphabet of human thought", that all of knowledge might be so systematized that every fact could be tagged with a code. Cf. Mortimer Adler's Propaedia {1}.

I was fascinated with the Dewey Decimal System, which was so helpful in locating books in the public library: if I could but memorize that, it would be proxy for mastery of all the knowledge it classified. In those days, taxonomy dominated biological teaching too. (I will not detain you now with the perils of misplaced confidence in low- dimensional, or insight-free knowledge. They need to be remembered when we try to extract "knowledge" from an expert, measure how much we have, and so forth.)

Although I was committed from a very early age to a career in experimental biology, while in college I was eager to have some understanding of the epistemological roots of science, and enrolled in several courses in logic and scientific method. At Columbia, I was fortunate to have some personal exposure to members of the philosophy department: Ernest Nagel, Justus Buchler, and James Gutmann. With their help, I read George Boole and Whitehead & Russell {58}, and tried to follow J.H. Woodger in his Axiomatic Method in Biology {59} -- an effort to express what was then known of genetics and embryology in the formalisms of relational calculus. Our factual knowledge was sparse enough; but apart from that, I wondered if we really understood our assertions when they were expressed in the jargon of empirical biochemistry. Axiomatic reformulations of biology are only just now returning to the scene {3, 54, 57, 47}. They make the intellectual demand of coping both with the formal logic and the molecular biology.

- 2) My first encounter with a "computer" was in 1941, in a lab for high school students sponsored by IBM {23}. My own instrument was a microscope; but one of my fellows was making innovative improvements on a punch card sorter/tabulator. It was an impressive manifestation of an electro- mechanical automaton, one that could certainly calculate more reliably than I could. It looked like fun. After the war, there was some publicity about the electronic machines, which I read at the level of Scientific American or Science. But my own next step was the IBM 602A, on which I practised in Fred

Gruenberger's course at Wisconsin, in 1953, in order to get some concept of programming, albeit on a plugboard! One could do statistics on this machine, as did some of my colleagues in applied genetics; but I had no comparable excuse to play with it.

3) That postwar period also saw the elaboration of information theoretic formulations of genetics. We were starting to say that genes encoded the information needed to specify protein structure. {14, 51} This style of thought and expression became more explicit in the period after 1953 {25} with the recognition of the implications of the Watson-Crick molecular structure of DNA {22}. It would be backward for anyone in my field to ignore this way of looking at the biological world. Then, Marvin Minsky came to see me in 1955 at Wisconsin at the behest of some mutual friend to discuss automata. I am sure I had already heard of some of his own work.

4) My own laboratory research was a very mixed bag of theoretical formulation and empirical encounter. I had been extraordinarily lucky on several occasions - but I didn't want to be a hostage to chance: should there not be a more systematic strategy of problem formulation? And if one could do that, problem-solving might be a throwaway. Serious questions about the rational direction of science were invoked around an examination of why genetic recombination in bacteria had not been explored 40 years earlier. {24, 60}.

5) Starting with the observation of Sputnik, and a conversation with J.B.S. Haldane in Calcutta in November 1957, I had set out to assure that fundamental biological science was properly represented in the programs of space research that were just emerging. The danger was that scientific interests would be totally submerged by the international military and propaganda competition. They have never gained first priority; they might have been totally excluded. These efforts were merely advisory and critical until 1960, after NASA had organized a Life Sciences Research Office and asked me to establish an instrumentation laboratory at Stanford. With Elliott Levinthal's able technical direction of the lab, we became actively involved in the conceptual design of approaches to test for life on Mars, at such time as there might be a mission. I know most of my colleagues thought that would be well into the 21st Century, as we were a decade short of the lunar landings. But the possibility of finding another branch of evolution was of such compelling scientific interest, the stake was worth odds I knew were very long.

Both the internal activities of the Instrumentation Research Laboratory, and design discussions with the engineering managers of spaceflight missions (principally at Caltech's JPL) brought us into intimate conversation with technology of automation, process control, communications and computer management. Furthermore, mass spectrometry soon emerged as a technology of choice for chemical analysis. It has enormous sensitivity, selectivity, and independence of prior bias as to the molecular species expected {33}. As we shall see, it also offered some special opportunities and challenges in computation.

In 1961, I was also invited to serve on a PSAC panel on the management of scientific information. Our report {50} gives modest support to the implications of computer technology, along with "reproducing and microphotographing equipment" for information storage and retrieval. However, I had become acquainted with Eugene Garfield, the inventor of Current Contents, and had helped him set up a trial run of the Science Citation Index in the field of genetics {38, 19}. That experience (with its overtones of the classification of knowledge for purposes of retrieval) was an early success in the use of computers in support of scientific research.

By now, I concluded that I would have to learn much more about computers, at a hands-on level. The opportunity was engendered by the evangelistic efforts of Al Bowker and George Forsythe to establish an intellectual and technical base for and broaden interest in computers throughout the Stanford campus. In company with the development of a new division, then department, of Computer Science, and of a campuswide computer center, elementary programming courses were organized. I enrolled in the BALGOL (Burroughs Algol) course given by Bob Oakford, over the summer, 1962. This had much of the flavor of a course in English for fresh immigrants, the class having a very broad distribution of age and of academic status, specialty and sophistication.

I quickly succumbed to the hacker syndrome, (and have suffered episodic relapses over the last 25 years).

This was reinforced by the relentless rectitude of the machine in rejecting my errors - always so obvious in retrospect. "Next time, next time I will master the **** system!" Well, I did shortly become reasonably proficient (eventually, in a range from assembly to higher level languages) mostly out of determination not to be made a fool. In those days, we had a B220 - which would match a fairly feeble PC today - as the first campus machine. Its operating system would accept decks of punched cards in serial batch mode, with output either from the printer or new punched cards. The usual turn-around time was about 12 hours. If you got to the computer room around midnight, you might get another pass by 2 A.M. The democracy and night-owl ambience of the batch system was a social mixer for several enthusiasts from wide-ranging disciplines. (I particularly recall Tony Hearn, who was starting his symbolic algebra system, REDUCE, on the IBM 7090). The impedance of a one-pass per day turnaround certainly did filter out all but the most enthusiastic. You also spent a lot of energy trying to simulate the machine in your own thought, in contrast to the casual, experimental mode -- "Let's see if this works" -- of today's interactive systems. This mode has unquestioned advantages; but it may weaken programming as a teaching discipline for logical rigor (except insofar as pure, unremitting failure teaches mainly discouragement.)

Our first applications included some that are pertinent to medical informatics, but not to DENDRAL, in areas of genetic epidemiology {6}, including a contract to produce the childspacing report on the 1960 census. When we discovered that "children" of some mothers were delivered at 3 month intervals, I again learned the familiar GIGO lesson, and a healthy skepticism for mass data repositories. Massive numbers do not take the place of quality controls on individual data entries. Some other inquiries, e.g. of intercorrelations of season of birth and birthweight with postnatal outcomes, taught us the difficulties of removing all the confounding factors. The usual "socio-economic status indicators" do not begin to exhaust the vagaries of stratification of human behavior.

1962 also marked the recruitment of John McCarthy to Stanford. We met around the computer room, soon discovered we had a common friend in Marvin Minsky. I had read Marvin's article on steps toward artificial intelligence in the January 1961, special issue on computers of the Proceedings of the Institute of Radio Engineers {46}, the first issue I received as a newly enrolled member (having joined at the urging of Lloyd Berkner, chair of the Space Science Board). That article and McCarthy's intellect and excitement gave me a sense of tangibility of the possibility of engaging in AI research. When he showed me his new DEC PDP-1 and its interactive CRT displays (viz., Spacewar) I reached the conviction that "computers were going to change the whole style of scientific investigation". This was not going to happen with card deck data entry.

We soon conspired in various projects to try to enhance the interface of computers with medical science. The most ambitious of these was an effort to attract Marvin Minsky to join the faculty of Stanford Medical School; but unhappily for us he decided to stay at M.I.T. We also began to talk about bringing interactive computing, via time-sharing, to Stanford, along the lines of Project MAC, which John had helped to design at M.I.T. These discussions ultimately led to the ACME and SUMEX systems, as we discovered that the NIH was able to fund research resources for health research through its Biotechnology Resources Branch. McCarthy's PDP-1 also led us to emulate it as a laboratory interface computer, and our IRL signed on as one of the test sites for the new LINC (laboratory instrumentation computer) whose development NIH was sponsoring. This was, of course, the forerunner of the DEC PDP-8.

Meanwhile, the IRL was getting more actively involved in mass spectrometry. Carl Djerassi had come to the Chemistry Department in late 1959, and we had developed a close personal and professional association around his academic research as well as his continued research direction of the Syntex Corporation. (Upon the company's relocation from Mexico City to new laboratories at Stanford Industrial Park in 1961, he asked me to advise on its establishment of the Syntex Institute of Molecular Biology.) He was an accomplished mass spectrometrists; and of course I leaned very heavily on him for the elaboration of this technology for space applications. Conversely, he knew nothing about computers, and I was eager to find helpful applications in the zone of our common interest. The IRL began to work on using the LINC to manage the formidable data management problems of real-time gas-chromatography mass-spectrometry {52}. One central problem was the efficient translation of mass numbers to molecular formulas.

As I reexamine that arithmetic play, it reveals some premonitions of the later work. So I will expand on it beyond the intrinsic worth of the solutions {29}.

The mass spectrometer is an instrument that converts molecules of a sample material into ions that are accelerated and measured one by one. Further, by a combination of magnetic and electrostatic fields, each ion can be sorted by its mass number. For the initial discussion, we will consider only the molecular ion, ignoring further processes of fragmentation. At low resolution, we take atomic masses as integers (H = 1; C = 12; N = 14; O = 16; etc.) If we find a mass number of 14, this might be composed of H(14), C + H(2), or N. H(14) is a monstrosity: we have valence rules (H ~ 1; C ~ 4; N ~ 3; O ~ 2) that limit how many atoms can be bonded to a given atom. The ambiguity already seen at $m = 14$ is of course greatly multiplied in real cases, like $m = 3675$, a number which reflects the bounds of current instrumentation. Our first problem is to calculate all the compositional isomers consistent with a given mass number. At this level, it is a knapsack, or change-making problem: finding all the ways coins of different denomination can be combined to add up to a given sum. In non-negative integers, this is a diophantine equation, viz. we seek all the solutions, (i.e. compositions in h, c, n, o) of:

$$h + 12c + 14n + 16o + \dots = m.$$

The brute force approach is a set of nested iterations,

for ($h = 1$; $h \leq Z$; $h++$); for ($n = 1$; $n \leq Z$; $n++$) $m' = h + 14n + \dots$
and test the m' sums for a match to m . One simplification is to augment m , $m'' = m + k \equiv 0 \pmod{12}$. We then eliminate c and find solutions in h, n, o that satisfy $(h+k) + 14n + 16o \equiv 0 \pmod{12}$. I would be interested to learn of deeper analytic approaches to the problem. For online computation, one thinks of constraining Z , at least by the mass still unassigned in each loop, to reasonable bounds. It transpired that the valence considerations also set constraints on possible values of h ; and other tricks allowed still further pruning of the tree generated by the nest, greatly shortening the computation.

Prior aides to mass spectrometrists had been published tables (embracing 570 pages in print) that reported the compositions sorted by m , from about 1 to 500, with n and o no greater than 6 {4}. A full set of tables for m up to 1000 would take about 10,000 pages of fine print.

In reality, the masses of individual nuclides are not integers (subject to the so-called nuclide packing fraction), and we have

$$H = 1.0078252$$

$$C = 12. \quad (\text{by definition})$$

$$N = 14.003074$$

$$O = 15.994915$$

With a high resolution mass spectrometer, a given ion might be reported as $718.374 \pm .006$. Hundreds of compositions would match 718 in integers. One should use the fractional mass (.374) as equally important information in limiting the search. We no longer have an equation in integers, owing to the instrumental error. Nevertheless, various arithmetic tricks were devised that took account of valence rules, plausibility of composition, the negative and positive packing fractions of O and N, and the abnormal proportional discrepancy of H, to keep the search down to a manageable scope. For paper and pencil work (in 1964) this was embodied in a handbook of some 50 pages, in which one could quickly look up the "mass defect" of numbers classified by residues modulo 12. {26} Even that small book was later {35} obsoleted by an algorithm that depended on a one-page table with just 72 non-zero entries, and a few arithmetic steps easily done on a 4-function hand-calculator. By then, however, most machines were coupled with data processors that were oblivious to such economies. (And mass spectrometrists no longer give much thought to the arithmetic of this problem.)

The main point is self-evident: contextual information could be incorporated early into the combinatorics, and reduce a blind generate-and-test search by very large factors.

We turn now to the larger frame of chemical analysis. Molecular ions are important targets for mass spectrometry; in the ideal case they can give unambiguous compositional formulas. Of course, they tell

nothing of the topological connectivity of the constituent atoms. To illustrate with a trivial case, $C(2)H(6)O$ has a mass of 46.041866 but this does not distinguish methyl ether (CH_3-O-CH_3) from ethanol (CH_3-CH_2-OH), a medically significant matter! Within the mass spectrometer, however, the molecular ion also breaks up into a set of fragments (according to reasonably well understood rules). The spectrum is the array of these fragments, revealed by their mass numbers. It is often an absolutely distinctive fingerprint, diagnostic of a specific structural isomer (as the molecular ion mass number is of the composition).

The elementary problem of inferring composition from molecular mass now well-solved, could we take the next step: model the chemist's inferential procedure in finding the structure from the spectrum?

How to represent organic molecular structures in graphs, and then their dissection into subgraph fragments, as occurs in the mass spectrometer; became my task for 1963-64. Emile Zuckerkandl, an associate of Linus Pauling, also visited my lab. during this interval. We started some of the first statistical studies on amino acid sequences of proteins, looking for hints of non-random regularities within sequences, and unsuspected evolutionary relationships among different ones. This is a substantial industry today {40}; there were not enough published data in 1963 to offer more than a few tantalizing hints.

6) All this was then the ideological context of my meeting Ed Feigenbaum on April 6, 1963. This was a Saturday meeting that Karl Pribram had organized at the Center for Advanced Studies in Behavioral Sciences on computer models of thought. John McCarthy, Ken Colby and several others were also present. I told Ed how I was groping for ways to represent chemical structures; he was already on the lookout for problem areas in science to which to bring his background on mechanized problem-solving. We stayed in good contact: I have a signed copy of "Computers and Thought" {15} dated 1/17/64.

During 1964, I completed the preliminary graph-theoretical work on representation of organic molecular structures. {30, 32, 28}. That had entailed going back to the elementary graph theory of the 19th century for canonical forms of tree structures {21}. Fortunately, George Polya had done some important work on generating functions in 1936 {49}, and was most generous in his advice about that older literature. When it came to cyclic graphs, I had a particularly entertaining time, almost at the level of recreational mathematics {31, 34}.

See Figure 1: Cyclic Graphs

For a century after the conception of organic molecules as ensembles of connected atoms subject to structural isomerism (Berzelius, 1831: {48}; Crum Brown, Butlerov and Kekule in the 1860's: {20}) no more than desultory attention was given to the formal mathematics of their representation as graphs, to the potentialities of a connection between Hamilton circuits, convex polytopes and organic molecules {53}. The topology was mostly too elementary to engage the interest of serious mathematicians -- but there are still intractable problems in the enumeration of cyclic graphs (after automorphisms!). Related issues, like the notorious map-coloring problem, illustrate the still primitive state of analytical approaches to the taxonomy of graphs. Cayley {12} made a stab (a fallacious one) at the enumeration of the hydrocarbons; this was improved upon by Henze & Blair in the 1930's {5}. In the mid-1960's, Balaban and his colleagues in Romania began their extensive investigations independently of the work at Stanford {2}.

Chemistry has then developed a taxonomy of its own structures that has no coherent mathematical theme. It is full of colorful but trivial names that give no structural information: a few eccentricities like "windowpane" for 4 fused rectangles are a partial exception. A formidable burden in learning chemistry is the enormous amount of rote memorization that is entailed in associating names like butane, cholestane, cytosine, melezitose, xanthopterin -- there are tens of thousands of these -- with graphic representations. One may think of these as the passwords for admission to the secret society; they do deter many a student, and they may also impair a critical analytical perspective about organic chemistry. These pictures also have formal names, but the nomenclatural handbook that gives the rules for their translation occupies a thick book, mostly the idiosyncratic cases.

Dendral-64 is a set of reports to NASA {30, 32, 28} that outlines an approach to formal representation of

Mappings of cyclic chemical structures
 onto trivalent graphs - convex polyhedra
 from Lederberg (1965)

VERTICES	FIGURE	POLYGON	FORM(S)	EXAMPLE
0		CIRCLE		BENZENE
2A		BICYCLANE		NAPHTHALENE
4A		TETRAHEDRON		TRIPHENYLENE
4B		TRICYCLANE		ANTHRACENE
6A		PRISM		PYRENE
8A		CUBE		CUBANE
8B		BI-PENTAGON		BENZOPYRENE
8C		BI-TETRAHEDRON		PERYLENE
10A		BI-HEXAGON		BENZOPERYLENE
10B				DIBENZO-CHRYSENE
10C				DIBENZO-PYRENE
10D				
10E		PENTAGONAL PRISM		ETHANEDIYLIDENE-CYCLOPENTA-PENTALENE

chemical graph structures, and a generator of all possible ones. Acyclic structures (trees) were readily tractable. Cyclic ones can be dealt with, mainly with the help of a few tricks that rely upon an empirical enumeration of the underlying vertex graphs -- this is feasible within the bounds of practical chemistry -- which is analytically unsatisfying. It helped to learn about Hamilton Circuits of graphs (paths that touch each node just once) {27}, since the enumeration of these, and the elimination of automorphisms are greatly simplified. When it came to the implementation of DENDRAL for (typical) organic molecules with imbedded rings, Harold Brown, Larry Hjelmeland and Larry Masinter provided the group-theoretic general mathematical solutions to these perplexities {10, 8, 7}. A few molecules have been constructed precisely because they defy some constraints of topological simplicity -- e.g. topological planarity, namely their connection graphs cannot be drawn on the plane without bonds crossing; as exceptions they make history and can be dealt with as such. {31, 55}

The DENDRAL generator was then designed so that only one canonical form of a possible automorphic proliferation is issued, greatly pruning the space of candidate graphs. This was the essential prerequisite for an AI program that could manage the generator and confront it with information derived from the mass spectrum. But I had no idea how one would go about translating these structural concepts into a computer program, nor whether this would be computationally feasible with available hardware. Even more telling, I had only second-hand access to the field of AI and barely knew how to relate these conjectures to the systematic approaches that were emerging {15}. It was fortunate indeed that Ed Feigenbaum came to Stanford just at this time: we promptly got together again and organized the collaboration that became the DENDRAL project.

Ed now deserves equal time in presenting his personal prehistory. Some of his oral history has appeared in McCorduck's book {42}. In addition, I have a few of his own words, excerpted from an electronic message:

Date: Thu 8 Mar 84 00:22:01-PST
From: Edward Feigenbaum <FEIGENBAUM@SUMEX-AIM.ARPA>
To: lederberg@SUMEX-AIM.ARPA
Subject: our history {*referring to some private notes*}

Josh, all of what you have written accords with my memory of things we discussed in 1965 as we quickly got to know each other better.

Your mention of mass spectral analysis as a problem domain in which we should work came as an answer to a question I posed you. I had decided that I wanted to work on constructing models of EMPIRICAL INDUCTION IN SCIENCE, within the methodology that I had learned from Newell and Simon, i.e. work on a concrete task domain, not in the abstract. So I needed a concrete task domain. You said you knew of one that contained the essence of the empirical induction problem, that you had been working on it for a while, you even had a computational algorithm underlying it (which immediately made me think: aha, legal move generator as in chess-playing programs). ALL of this conversation (embryonic research planning) took place AFTER I arrived at Stanford Jan 1, 1965, but I remember that I would not have sought you out for advice on the aforementioned puzzlement had I not met you earlier [April 1963] and learned of your interest in machine models of thinking. Recall: there were very very few people to talk to about machine models of thinking at Stanford in early 1965.

We didn't just "bump into each other" as in "lucky accident". You

weren't at the [April 63] meeting by "lucky accident". I didn't decide to work with you on the mass spec analysis problem because it was of general intellectual stimulation. You had a definite interest in AI and I had a definite interest in hypothesis-formation/theory-formation. (Incidentally, do you remember how we went round and round on whether to deign to call what DENDRAL did "theory formation"? We decided on "hypothesis formation" to distinguish the case of one spectrum being explained by one (or a few) structures. We reserved the use of the term "theory formation" for a later date, for a more general approach, and decided to use it in describing Meta-DENDRAL (many spectra--> rule set).

P.S. Some things do appear to be "lucky accidents". It would appear to be a genuinely lucky accident that I chose to go to college at Carnegie Tech (an accident of Westinghouse scholarships and my family's financial condition), and a lucky accident that I met Herb Simon through Jim March, and that Herb paid attention to me, and that the Logic Theory program was invented while I was still a Carnegie Tech undergrad and that I was taking a seminar from Herb at the time of its invention. One level deeper: I was an ACTIVE RECEPTOR SITE re the idea of a computer. I had never even heard of an electronic digital computer before Herb handed me an IBM 701 manual, but... I had been entranced by mechanical calculator machines in high school and before. My father was an office manager/ accountant and owned a giant, heavy Monroe or Marchant calculator. I became an expert on its use. I even remember dragging it with me miles on the bus to Weehawken High School, heavy as it was, just to show off my skill with this marvelous technology that no other kid in the high school knew anything about. So when Herb gave me that manual, he was projecting me five or six orders of magnitude into a territory I was already fascinated with. It was also very fortunate that my introduction to the electronic computer was via the computer as general symbol manipulator (Herb never mentioned that it was anything BUT that) and that my introduction to programming was via IPL 1 and 2. (I might add that such a sophisticated early view, given to me by Herb and Al Newell, has taken away most of the awe from later developments; everything else has seemed to be "merely" extensions of the great inventions and discoveries of the 1956-59 period) "

END OF MESSAGE

It is now Spring 1965, and our project is concretely launched. Ed and Richard Watson circulated a bulletin {16} "An initial problem statement for a machine induction research project" to graduate students in Computer Science; but it was to take a few years of slow accretion to organize a cadre of collaborators. One of our first, Research Associate Georgia Sutherland did a fabulous job on the formidable task of converting the concepts of DENDRAL-64 into a LISP program, interleaving its production with that of a baby: an early prototype of telecommuting. Her first report was issued February 1967 {56}: we finally had a working program with which we could all experiment with heuristics and other measures to bring its performance to practically useful levels. The choice of LISP was originally mandated by the good match of its data structures to trees, to the sparse connection tables of chemical structures. But the memory and bit crunching requirements were of course monumental -- it's a wonder we got as far as we did with the hardware of the time. I used to remark, in arguments with

ideologues, that in the last analysis it was the programming environment of INTERLISP that was its key advantage.

We were fortunate to have continued support from NASA and from DARPA to continue these explorations. We had quickly found that the campus IBM 7090 had too little memory to support our LISP programs; and we were eager to move to more interactive systems for program development. In 1966, our DARPA sponsorship gave us access to the Q-32 time-sharing system at System Development Corporation (Santa Monica) with a 100 baud teletype interface. My first experience with remote, time-shared hacking was a happy vision of future improvements. Then, John McCarthy acquired a DEC PDP-6, and we approached something closer to the modern era. Bruce Buchanan joined our group, and we had great benefit from his philosophical perspective, patience, insight and administrative acumen. We had more and more collaborators, including the explicit involvement of Carl Djerassi and his associates as founts of authentic chemical expertise. As our reports began to appear in refereed chemistry journals, we eventually gained some confidence that we were contributing to the scientific domain, as well as to system-building -- a point about which some of my colleagues had been skeptical. Broader access to these computer applications became possible with the help of the NIH-supported computer resources: ACME, a general time-sharing system for the Stanford Medical School, and SUMEX-AIM, a national resource to support research in artificial intelligence in medicine {11}. However, as this account is now moving into a time of documented history and numerous publications {41}, I omit many details.

The program was being crammed with more and more chemical information, and becoming an effective assistant in the analysis of spectra and other analytical information. Buchanan recoded DENDRAL's knowledge of mass spectrometry, originally embodied in a collection of LISP procedures, into a table of explicit rules separated from the internal operations of the system. This redesign to facilitate augmenting, validating and editing the informational (i.e. rule) base, was a paradigm shift later to become the standard for expert systems. Balky resistance of the program to input of new ideas remained the limiting factor in its elaboration. At every weekly group meeting, a dozen new ideas would come up: but we knew that each one would take weeks to implement in tested software code, just to test it. Natural intelligence still enjoys a flexibility of hierarchical planning yet to be achieved in machine emulations {17}.

Throughout this time, we would ask ourselves the nagging question: was the growing pragmatic success of DENDRAL in solving chemical problems teaching us anything about artificial intelligence? Had we simply crafted a special case, accumulating a hefty store of chemical knowledge from several experts? We did see the need for -- and Bruce Buchanan made a stab at -- a self-learning system, whereby META-DENDRAL could induce its own rules (as the chemist does) by introspecting about concrete data inputs of mass-spectral fragmentation of molecules of known structure. This showed real promise {10}, but was impeded by the insufficiency of computer horsepower needed when DENDRAL itself had to be invoked repetitively to test every new rule candidate induced.

We never got a grip on one idea that I hope to return to someday. DENDRAL is remarkably neatly structured (as implied by its name) as a generator of trees of candidate structures {39}. These can easily number in the billions or more, in practical cases: the efficiency of the program depends on the pruning of impossible or implausible cases, as early as possible; preferably large branches at a fell swoop. The order of application of the shears can have a large effect. To give a stupidly trivial example, if N (nitrogen) is absent, we don't generate molecules that may contain N, then retrospectively eliminate each of those twigs. We gave some forethought towards optimizing the sequence of shears; but we know this will be case-specific, sometimes in ways we have difficulty predicting. We should build in recurrent introspection about the shearing sequence, make that a specific planning objective, and experiment with it from time to time. These considerations (I called it Theta-DENDRAL for reasons not recalled) would have broad generalizability to rule-based systems: the sequence of invocation of rules is often totally inaccessible to the user, and rarely if ever (as far as I know) is it dynamically regulated.

We did do some work on the interesting tradeoffs between storing memory of all partially completed branches, vs. regenerating them as needed. Finally, we had many discussions of the desirability of learning to read expertise from the world's published books, to bypass the oral tradition. The ultimate fantasy was to attach a high-order DENDRAL directly to a mass spectrometer, learning directly from

Nature.

I wish I had the documentation, but I have an image of a conversation when I was pressing Ed about the limitations of DENDRAL as general intelligence: he responded with the illumination that I may paraphrase: "That's exactly the point! Knowledge, not tricks or metaphysical insight, is what makes the program effective -- and that itself is an insight of general import." That is why I remark, we were trying to invent AI, and in the process discovered an expert system. This shift of paradigm, "that knowledge IS power" was explicated in our 1971 paper {17}.

Shortly thereafter, Bruce Buchanan and Ted Shortliffe initiated the MYCIN project {9}. As Alan Newell remarked (in his preface to {9}), MYCIN had no pretensions to deep theoretical structure of chemistry, none to outdoing the experts, but only to conveying that expertise as advisory to the general practitioner (in optimizing the prescription of antibiotics.) Their coding of MYCIN gave a fresh start to the design of rule-based systems that could be readily transported to other applications.

The published documentation after this time is quite rich, and I will refer to that for further historical development. Time now for the numerous morals of the story.

Most problematical is the public utility of private autobiography. But biography remains very popular, albeit the main lesson may be the very idiosyncrasy of personal history and character. Worse than no history would be a false conception of it, that it has rigorous rules. As my tale shows, chance does play an enormous role in bringing together people, ideas, situation in a productive way. Were we lucky? Who knows what the alternatives might have been?

One lesson of personality should be brought out, especially when the media enjoy characterizing the scientific enterprise as rapacious competition and selfishness. The fraternity that came out of the DENDRAL effort was a high in my life experience, matching the gratifications of scientific excitement and (perhaps belated) recognition. One is not always so lucky in one's colleagues; but we should not glamorize and confuse the pathology as the standard.

The project also dramatized the values of electronic communication in project management. Although we certainly met informally from time to time, most of our serious communication (be it a few yards down the hall) was by electronic mail. In this way, innumerable proposals and drafts could be posted on common bulletin boards, and subjected to consensual review, often through scores of cycles of reiteration. Distance was no consideration, courtesy of the ARPANET, and communication could be sustained during momentary travel, and collaboration continued when participants moved. (This ms. will of course be shared between the Rockefeller and Stanford.) Such draft texts, program modules and outputs needed critical scrutiny of a kind that is only possible when one has a copy of the file to work on from one's own terminal. I went so far as to characterize this mode of communication "The New Literacy", and I meant it {37}. Databases should not be thought of as static, final repositories but as bulletin boards, subjected to dynamic critical attention by the entire knowledgeable community.

Stanford University, in the 1960's, was a fortunate place to be for the pursuit of scientific innovation, and equally for a highly interdisciplinary program. Computer science, medical science, chemistry, were all in a surge of rapid expansion and new opportunity. If there were no specific facilitations for these kinds of interactions, nor were there rigid impediments. There were potential problems of disciplinary homes for the degrees sought by graduate students; but in the event we never found any students who looked for a degree in what might have been a difficult hybrid of say genetics, chemistry and informatics. The graduates in the project were able to justify themselves by the standards of the major department. The laissez-faire philosophy of the institution worked admirably, so long as we were able to secure funding. While we had the usual share of crises, we should look back in awe at the forbearance of the three agencies, NASA, DARPA and NIH who did make significant risk investments in a novel venture. Needless to say, all of the senior professors were also staking their credibility in the process. There is no guarantee that untenured faculty would have been able to feel so secure.

The greatest hurdle in efforts to replicate the experience would be to find experts willing and positioned to

be able to forego continued immediate productivity in their own fields, for the sake of longer term ends in system building. Students and fellows may be intimidated by the demands of working across disciplines, and some were concerned that there would be a limited market in say artificial intelligence in molecular biology. Their prudence may be pragmatically justified. The process of knowledge extraction is unbelievably arduous: as always, 90% of the effort must go into debugging and validation. The process can give the expert an opportunity for critical self-reflection about the foundations of the scientific domain. Some of the return on investment of DENDRAL was in its motivating a fresh study of the conceptual structure of organic chemistry, apart from its actual application in computer programs. This is to be commended in problem choice in other areas of application, scientific or otherwise.

The choice of organic chemistry and mass spectrometry as an object domain was a matter of careful reflection. I might have preferred molecular genetics as more germane, and closer to my own experience. But in 1965 I did not feel it had ripened sufficiently to allow a secure theoretical framework for the necessary deductive tests of candidate hypotheses. (By 1975 it had, and this perception was the root of the followon MOLGEN project {18}). In his 1961 review, Minsky had been rather critical of generate-and-test paradigms: "for any problem worthy of the name, the search through all possibilities will be too inefficient for practical use." He had chess playing in mind with 10^{120} possible move paths. It is true that equally intractable problems, like protein folding, are known in chemistry and other natural sciences. These are also difficult for human intelligence. The heuristics we have evolved biologically tend instead to relate to real world faculties like speech and image recognition. Nevertheless, solution spaces of 10^6 to 10^{12} candidates are both interesting and feasible challenges to computation, and many are of scientific or technological consequence. Our particular problem in chemical analysis is one of exhaustive elimination, to find ALL solutions that match the spectral data set. Further measures may then be needed for a final disambiguation. Theorem-proving is a reasonably good analogy. Our chemical heuristics are second order: to find efficient ways of rigorously pruning the search tree, though it can be helpful to find a single approximate solution from the most plausible genera of chemical structures (e.g. rings limited to 5 or 6 nodes) and examine ways in which it can be altered and give the successfully matching spectrum. Whatever heuristics are used, no search branches can be discarded without the rationale being transparent to the chemist. Unlike chess or image understanding, chemistry does have an intrinsic mathematical structure that permits its move generator to heed the constraints of the data, so that efficiency is more readily achievable. And we have criteria, both for a formally correct candidate (a graph in canonical form), and to know when it is a solution, i.e. the test generates a spectrum that matches the data. We played against Nature. In chess (and in war), you have to play against another "expert".

Other areas of natural science deserve a fresh reconnaissance to inspire a reexamination of their conceptual structure. Biology, in particular, will soon suffocate in the sheer bulk of knowledge about DNA and protein structures, and the complex interactions of the causal chains they initiate, unless new epistemological machinery can be invented.

Finally, I would remark that I have never viewed research on artificial intelligence as having much bearing on how the human brain functions: there are too many differences in architecture and in levels of complexity, connectivity, and programmability. Nor do I see how neurobiology has contributed very much to AI. At the highest level of problem-solving routines, expert systems do of course exploit human experience. My interest in AI has little to do with my background as a biologist, a great deal with curiosity about complex systems that follow rules of their own, and which have great potentialities in preserving the fruits of human labor, of sharing hardwon traditions with the entire community. In that sense, the knowledge-based-system on the computer is above all a remarkable social device, the ultimate form of publication.

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Appendix:

This memo is an excellent snapshot of the status of AI research as seen in 1965, and will therefore be appended in its entirety.

STANFORD ARTIFICIAL INTELLIGENCE PROJECT
Memo No. 30

April 5, 1965

AN INITIAL PROBLEM STATEMENT FOR A MACHINE INDUCTION RESEARCH PROJECT

by E. A. Feigenbaum and R. W. Watson

Abstract: A brief description is given of a research project presently getting under way. This project will study induction by machine using organic chemistry as a task area. Topics for graduate student research related to the problem listed.

The research reported here was supported in part by the Advanced Research Projects Agency of the Office of the Secretary of Defense (SD-183).

We are engaged, in conjunction with Professor Lederberg of the medical school, in a research project which offers possibilities for graduate research, both well defined problems suitable for C.S. 239 projects and not so well defined problems suitable for Ph.D thesis topics. In this memorandum we will define the problem briefly and then outline some suggested projects. If you are interested in any of the projects or topics suggested, or have a topic to suggest related to this project see either of us for further details.

The long range goal of this research is to attempt to come to grips with the problem of induction by machine. That is, how does one build a machine (write a program) which can interact through a suitable interface with its environment and build and improve models of the environment.

The specific task area chosen in which to attack this problem is organic chemistry and in particular, the determination of the structure of organic molecules from mass spectrograph data. The problem presently facing a chemist is roughly the following:

- 1) A quantity of an organic molecule is supplied to a mass spectrometer.
- 2) The molecules are bombarded with electrons which break up the molecules into ionized subparts.
- 3) The mass spectrometer outputs a spectrum (i.e. a distribution of the masses of the subparts).
- 4) The largest mass in the distribution which occurs in any quantity above a given noise level is that of the parent molecule.
- 5) By trying various combinations of atoms the chemist finds molecular compositions which have a mass equal to that determined in 4. If the resolution of the mass spectrometer is fine enough the determination of a unique composition is possible.
- 6) Once the chemical composition, or possible compositions, of the molecule is determined, the chemist uses various heuristics in conjunction with the mass spectrum to determine the structure of the molecule.

The computer science problem is to automate the above process. At the present time we see the project as progressing in the following stages.

Stage 0 - Display of Chemical Structures

Professor Lederberg has developed a linear notation for organic molecular structures. Further, he has

devised an algorithm which given a chemical composition as an input will produce as an output all topologically unique organic structures corresponding to this composition. The system is called "Dendral" and exists as an Algol program for the B-5000 written by Larry Tessler.

At the present time many of the structures are not chemically meaningful. Therefore, our first task will be to develop a system which will interact with a chemist and the Dendral system and determine rules for chemically meaningful structures. These rules will be automatically incorporated into a "filter" for the Dendral system.

Presently a program for the PDP-1 exists which accepts a linear Dendral string and displays a chemical graph on the Philco scope. The problem then of Stage 0 is to improve this program and to develop the software for tying it in with Larry Tessler's program through the disc and which will allow us to use LISP on the 7090 from the Philco scopes.

Stage 1 - Chemist at the Philco Keyboard

During Stage 1 we will develop the programming techniques which will allow a dialogue to take place between the chemist and the system for growing the filter on the Dendral output. This system will involve the display of a graph and the chemist's determination of whether or not it is chemically meaningful. The system must then question the chemist to find out what rules the chemist is using for his determinations and accept his answers in a suitable language. In general, the chemist will not be explicitly conscious of the rules he is using and the machine will serve the important function of helping to bring these rules to a precise awareness.

The end result of Stage 1 is that we will have an improved Dendral system and have learned some important and useful computing techniques. An improved Dendral system and associated display should also be of value to those interested in the problems of information retrieval associated with the chemical sciences.

Stage 2 - Mass Spectrograph Analysis

In stage 2 a chemist and a machine interact in real time through the medium of a scope, scope keyboard, typewriter and possibly light pen or tablet. If the machine were used strictly for performing clerical and algorithmic processes the following dialogue would result.

- 1) The machine would be supplied with the mass spectrum and would display on the scope face a histogram and the chemical composition(s) of the molecule.
- 2) The chemist using his experience and peripheral information would then input a linear description of a trial structure which would then be displayed on the scope as a chemical graph, or the Dendral system would be invoked to systematically display chemical graphs which correspond to the given composition.
- 3) The chemist, using his knowledge of likely places for breaks to occur in the above structure when under electron bombardment, would indicate such a break on the graph. The machine would then compute the mass of the subparts and indicate whether or not such a mass exists in the histogram. Or, the chemist would indicate a mass number in the histogram and the machine would indicate whether or not a subgraph exists which has this mass and if it does exist indicate which subgraph it is.
- 4) The chemist may also want to move various subgraphs from one place to another and then proceed as above. The machine will then compute the linear canonical form of these new graphs and possibly change the display to a canonical form. Further, the Dendral system may be invoked to systematically change a given subgraph.
- 5) The chemist eventually finds a structure which he hypothesizes as capable of yielding the mass spectrum.

What we want is for the machine to be used not only for clerical work, but more importantly to learn from the chemist's behavior and therefore take over much of the analysis on its own. To this end we visualize the following variation of the above dialogue.

Initially the machine would be input the correct structures corresponding to different chemical compositions. The chemist would then proceed to present an example analysis of this structure in conjunction with its mass spectrum; finally concluding with the known result that the structure could have yielded the given mass spectrum. During this process the machine will probe the chemist for the rules leading to his behavior. The machine will incorporate these rules in a data structure which will allow the machine to perform a similar analysis.

The machine will then be given a chemical structure corresponding to a given mass spectrum and will be asked to proceed on a step by step analysis of its own. The machine will report its "reasoning" to the chemist as it proceeds. When the machine makes an incorrect step the chemist will interrupt and a dialogue will take place until the machine can make the correct step.

Finally, when the machine can correctly analyze structures known to correspond to given mass spectrums the system will be given a composition and the Dendral generator will be invoked to systematically present for analysis possible structures. Then a dialogue of the following type will take place. The machine will proceed with an analysis as far as it is able and then the chemist will take over. As the chemist manipulates the graph with machine aid, the machine queries the chemist for the rules governing his behavior and a dialogue takes place.

Eventually the chemist reaches a hypothesis that the given structure could or could not yield the given mass spectrum. The machine then proceeds to analyze the structure on its own to see if it would reach the same hypothesis. If not, a further dialogue takes place until the machine can reach the hypothesis of the chemist.

When the machine seems adequate at this task we proceed to Stage 3.

Stage 3 - Good Initial Guesses as to Chemical Structure

In stage 2 the man and machine proceeded systematically through the structures produced by Dendral. Clearly for any large structures the number of isomers of a given chemical composition could run into the millions. Therefore, the chemist must make a good initial guess as to a possible structure and only rely on the Dendral generator to modify subgraphs. Again the chemist and system interact, with the machine querying the chemist to determine the rules for proposing initial structures. The procedures to be followed will be similar to those of the previous stage.

Stage 4 - Refinement of the System

When stage 3 is completed the system will be a good mass spectrum analyzer. However, the data structures produced during this stage will be complicated, duplicated and in general unlikely to be optimum. Therefore, the program and associated data structures which result from Stage 3 will be carefully analyzed to determine how to write an efficient compact system and to determine which sections contain general chemical knowledge and which contain knowledge of a specialized character, useful mainly for mass spectrograph analysis. The final efficient program which results will form the software for some experiments to be undertaken by a suggested man probe and the efficient program minus the specialized structures will form the basis for a system to be applied to some other chemical tasks such as the synthesis of organic molecules.

The following problems suggest themselves as possible research projects.

1. Display Problems:

In order that the display of the chemical graphs be as useful as possible to the chemist, it should

display the graphs in a form as close as possible to that to which the chemist is trained. This task is difficult to do automatically with our present experience. Therefore, one possible approach at this time is to develop a system which automatically displays a graph close to that desired by the chemist and then allows the chemist to manipulate substructures by simple rotations and bond length adjustments. Another possibility is to allow the chemist to "draw" the graph from the keyboard or with a light pen when it is available.

Because of the size limitations of the scope face it will not be possible to display large molecular structures in their entirety. Therefore, it would be useful to have a "window" mechanism which will allow the chemist to study subsections.

Other features are needed which will allow one to save displays, display more than one graph at a time and perform text editing on the linear input. It would also be useful to allow the chemist to build an initial structure and to later make insertions and deletions as well as move a given substructure to another point on the graph.

As the work on the display proceeds feedback from chemists will indicate other useful refinements to the display system.

2. Various programs need to be written which will allow us to use the facilities of the 7090 from the Philco keyboard.

3. Problems relating to Dendral:

Dendral is a system for canonical representation of chemical structures. However, the chemist is usually not trained in this system and would probably find it easier to input a non-canonical linear string. Therefore, it would be of value to have a routine which would convert this string to a canonical one.

Other more abstract problems relating to the Dendral generator are supplied by Professor Lederberg in appendix A.

4. Mass spectrograph analysis problems:

The chemist will want to have a histogram displayed or some display containing equivalent information. The chemist will further want to indicate a given mass number and have the system determine whether or not there is a subgraph with the indicated mass. The work on this problem will lead to abstract on the searching and comparison of list structures.

It will also be of use to the chemist to be able to indicate a given bond as a likely place for a break to have occurred when under electron bombardment and have the system determine if the masses of the subparts are in the distribution. The chemist will also want to be able to invoke the Dendral generator to systematically mark and change subgraphs.

5. The Dendral filter growing problem:

As mentioned before, the Dendral generator will generate all topologically unique structures regardless of whether or not they are chemically meaningful. The problem here is to grow, on-line, a filter which will only allow chemically meaningful structures to be displayed. To solve this problem, techniques need to be developed so that the chemist can be questioned for his rules of chemical meaningfulness and so that his responses can be dynamically incorporated in a changing data structure. Because the chemist will not always give correct rules, methods must be introduced to guard against the possibility of incorrect rules permanently entering the system. Persons interested in natural language and the computer or formal languages may be interested in this phase of the work.

6. Advanced mass spectrograph analysis problems:

Related to the problem above will be the development of techniques which allow the rules supplied by the chemist for analyzing structures to be directly introduced into an internal machine structure. This structure will allow the system to perform the same functions as the chemist and report to the chemist the important stages of its analysis. The detailed problems in this area will only become clear as we proceed.

It would seem to us that the problems related to the display are the most suitable for M.S. projects as they are quite well defined. The more challenging problems related to the Dendral system and filter and Stage 2 would seem to be of the greatest interest to those contemplating doctoral research.

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APPENDIX A

A number of problems in combinatorial graph theory, abstract groups, symmetry, and related subjects have arisen. Some of these would contribute to the elegance and efficiency of the DENDRAL system. Other questions are more abstract and have been suggested by the chemical graphs.

- a. Enumeration of cyclic trivalent graphs. This includes the polyhedra. Grace (a former Stanford Mathematics graduate student) has done a possibly vulnerable enumeration up to the 18th order.
- b. Efficient test for isomorphism and reduction to canonical forms.
- c. Programming to anticipate symmetries and avoid retrospective elimination of isomorphs.
- d. What is the least polyhedron lacking a Hamilton circuit?
Now known $20 < n < 46$.
- e. Generalization of the Hamilton circuit (in the sense of mapping a graph on to segments of a circle) to mappings on higher order figures. In DENDRAL-64 the treatment of non-Hamiltonian cyclic graphs * remains somewhat messy.
- f. Heuristic approaches to finding a Hamilton circuit of a graph.
- g. Enumeration of graphs with some 4-valent vertices. In DENDRAL-64 this is also somewhat messy, being treated by the collapse of 4-node circuits into 4-valent nodes.

Planting the Seeds

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I started thinking about computing in 1948 when I first became intrigued by the book *Cybernetics* by Norbert Wiener, and problems of respiration in exercise. The combination of problems was too complicated to deal with symbolically and I wanted a physical representation of the mathematics involved. Such considerations found me firmly embedded in computing by the mid-fifties. By happenstance, I found myself giving a presentation at UCLA on a Sunday morning to a group at the Brain Research Institute. Apparently, because of my interest in neural computing, or perhaps because I had the temerity to cite scriptures on a Sunday morning in a scientific session, Dr. Bruce Waxman invited me in 1963 to join the ACCR which was an ad hoc committee to promote medical use of computers in research.

It was for me a most marvelous committee and my first opportunity to deal publicly with the great figures of that day in computing. Many are here and on the panel, including Dr. Waxman himself. I would characterize myself as a passive observer in most of my life, and thus I had the privilege of being on the committee with Drs. Lusted, Pratt, Warner, and Dixon of the medical area; and the informative and amusing discourse they had with the likes of Norman Shapiro, Max Woodbury, Allen Newell, Joseph Weizenbaum, and Allen Perlis. The ACCR committee had as its mission the planting of the seed literally to develop the NIH portfolio in computer research in medical institutions. Our concern included physical facilities, machines, methods, ideas, and the laboratories where computer use was possible. You must realize, also, that even in the business and administrative sectors, computers in the early sixties were more in the stance of promise than production.

Planting the seed was a marvelously exciting activity. Machines changed. The LINC was promulgated, and transistorization and integrated circuits appeared. Early on computer research seemed enormously expensive. Also it was fraught with both difficulty and unexpected consequences. As a scientific panel, ACCR reviewed grant proposals, and also engaged in lengthy discussions about what was or was not feasible. Everybody was an enthusiast of a type which today is called a "hacker".

I can still recall being on an airplane, I don't remember where, but it was undoubtedly to or from a site visit, with Homer Warner. He, in addition to all the materials that a site visitor usually has to carry around, was carrying around some printouts and program consequences of early work that he was doing on pediatric cardiology diagnosis. We spent much of our flight time looking at printouts. Everyone had a very parochial interest. Mine were signal processing and mathematical representation. Becoming a member of ACCR to serve my government, as it were, was an exciting adventure, a privilege which has changed me in a manner from which I have not recovered. Most of the people on that panel and study sections over the years seed every section that meets for this symposium on medical informatics. Computing now brings us together to review this history. Interest in computation has brought together one of the most exciting adventures in modern science and philosophy -- the reification of ideas.

I would like to make only one contemporaneous comment about this experience. When it began, it was largely concerned with simple problems in representation, numerical computation, the acquisition and disposition of biological signals, in the use of statistics as the basis for inference, and the several forms of management information. I don't know to what extent these areas are now enclosed in the rubric "medical informatics". I have the unfortunate feeling that that rubric and its practitioners tend to focus too heavily upon what is now regarded as knowledge engineering or symbolic data processing, and have grown away from things which charmed others of us around this conference site. De-emphasized by our times are physical or biological signals, the operation of the health care enterprise, and its information systems for a reportorial, fiscal, and man-

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agerial point of view. We have become preoccupied with what we call ourselves and what constitutes an orthodoxy.

In those early days, I must say, every idea was new. Impossible ideas were the most amusing: everybody was at the same primordial state. Planting seed, I think, in many ways is more exciting than harvesting the fruit. Although we should not claim that today we are harvesting a great deal of fruit, the trees are sturdy saplings and there is much yet to come. Unhappily, I don't think we shall ever be able to relive those early days when Dr. Waxman, in particular, actually used to effervesce with the idea of giving away our dear Uncle Sam's money to someone who wanted to compute in the medical sector.

PLANTING THE SEEDS

BRUCE D. WAXMAN

IN THE BEGINNING

Reminiscing over biomedical computing 25 years ago is much like recalling one's prenatal impressions: There is also a temptation to invent examples of inspiration post facto, testifying to one's gifts of insight. Nevertheless, a few early recollections have that childlike aura of remembrance, are not immodest, and may be worth sharing.

One such was a quite accidental attendance at a mathematics society meeting at the Pennsylvania State University. The date, 1956, and the speaker, Dr. Grace Hopper. She told stories of the early days of computing for which she has become so famous. You have all probably heard them before. The recollection, however, is not so much of the specifics of these stories, but of being told of enormous power to process data and study relationships. The excitement remained dormant, residually stored in my subconscious, and then, in 1958 when consulting for Dr. Ruth Whitmore, a pediatric cardiologist at Yale, the Hopper experience emerged, full blown. Ruth Whitmore was the only pediatric cardiologist in Connecticut at the time, and in great demand. Finding a mechanism for more broadly sharing her particular expertise was very tempting. It seemed feasible as a minimum to automate her skills at EKG interpretation. What was not known was that Bob Ledley and Lee Lusted had already suggested the potential for computer aided diagnosis and Cesar Caceres had recently embarked on a program to automate the interpre-

tation of EKG's. You are all aware that EKG interpretation techniques are now commonplace; almost any local hospital will have such capability neatly bundled in the EKG machine's microprocessor.

The preoccupation with automated medical diagnosis persists and has spawned a great deal of activity in artificial intelligence. Incredibly, the initial and still very tentative work in medicine has been used as justification for a vast array of activities in military and intelligence applications. Clearly it is appealing, just as it was to imitate Ruth Whitmore's skills, to capture in a computer program the expertise fundamental to scarce and time consuming tasks. What is objectionable and distracting, is labeling this form of computing intelligent, with the implication that machines are capable of human cognition. I had no idea, in those early days when my office supported Lederberg's original work, that it would take off quite the way it did. Unlike the current preoccupation with AI, what Caceres did in those early days was highly reductionistic, dealing only with those empirical data that could be manipulated by straightforward mathematical/statistical techniques - undoubtedly why he was so successful. There was no mystique!

In 1960, Dr. James Shannon, then Director of the National Institutes of Health, created an Advisory Committee on Computers in Research. The impetus was from the National Academy of Sciences which had advised Shannon to explore the potentiality of computers in biomedicine. The members of that committee shared high enthusiasm for their mission and in the course of two years managed to spend over 50 million dollars on computer related biomedical research. As Executive Secretary of that committee, under the leadership of Lee Lusted, I shared in the great excitement and opportunities of those times. No one, certainly not Dr. Shannon, had intended anything of that magnitude, and when the N.I.H. hierarchy

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awoke to the reality of these expenditures, the committee was summarily chastised. By this time, however, the field of biomedical computing had been established and developed momentum of its own. Work prospered undaunted by the bureaucracy. The research supported by the committee's recommendations are quite well chronicled in the four volume series by Ralph Stacy and myself, Computers in Biomedical Research, Academic Press, 1965-1974.

A particularly rewarding sequel to this series of events relates to the sponsorship, by the aforementioned committee, of the LINC computer. Twenty years later, in a gala attended by everyone including the Secretary of Health and Human Services, the current Director of N.I.H. and just about everyone else that had anything to do with the development, the LINC was heralded as the undisputed progenitor of the minicomputer - a circumstance for which N.I.H. can take great credit!

LATER

By the mid 1960's enough had transpired for a few of us to become a bit philosophical. At least one recurrent theme, espoused by Bill Yamamoto, views strategic planning for research much like the process described by Asimov in his Foundation Trilogy. The point of the Asimov/Yamamoto injunction is that those creative enough to do pioneering work are unlikely to find immediate acceptance for their ideas. There is too much inertia associated with conventional wisdom. Acknowledging this, members of the Second Foundation (an Asimov literary construction) consistently attempt to deliberately and unobtrusively "Plant the Seeds" of change in the present with the expectation that their effects will emerge later.

There are numerous instances of individuals and institutions that were either totally negative or skeptical about the use of computers in medicine and biomedical research. The processing and analysis of clinical laboratory data by computer was suspect early on because it was believed that it would lead to a totally unjustified use of such tests. Use of CT scanning was vigorously questioned because of its expense and the lack of clinical validation. There was concern that every hospital in the country would want one when presumably such instruments should only be located at so called "centers of excellence". Similar skepticism was associated with automated hospital information systems, patient monitoring and various radiological systems. These technologies are now so much a part of the normal clinical regimen of diagnostic tools, so common

place, as to cause bewilderment that they were once highly controversial.

It is not possible to look back without giving great credit to Larry Weed and his PROMIS system which so revolutionized thinking about medical record systems and, more generally, the rational administration of medicine. For those of you who wonder what ever became of PROMIS, the National Cancer Institute's PDQ system, an absolutely elegant spinoff, provides encyclopedic information on all forms of cancer treatment.

Will Larry Weed ever forgive Octo Barnett and myself for COSTAR? It is not problem oriented (except in a most limited form), it certainly does not have the conceptual elegance of PROMIS, and yet at this writing there must be 300-400 COSTAR systems around the world. While specific evaluations may not have been conducted elsewhere, in the California health clinic environments COSTAR was a major factor in mitigating the cost and rationalizing the delivery of medical care. At another level, data produced by several San Diego based COSTAR systems provided the statistics needed for designing a highly revolutionary (and subsequently successful) plan for financing medical care for indigents.

MORE RECENTLY

In 1979, when I wandered out to San Diego to install and supervise the dissemination of COSTAR, I renewed my acquaintance with Bob Livingston who I had worked with in 1964 at NIH. Bob invited me to spend some time in his laboratory when I wasn't busy peddling COSTAR. In his letter of invitation he said something about being glad to have my brains in his lab. Now, Bob's lab has all kinds of brains laying around in jars! Eventually I convinced myself that he wasn't being literal, and spent, on and off, a very happy three years thinking about brain mapping.

What Bob was most excited about then, and still is, might be called his "Colombian" view of biology. He understood long ago, in a very profound way, that the biological world is three dimensional. It bothered him that most biological research, while occasionally giving lip service to the third dimension, rarely directed research in that direction. He kept saying again and again that the really important aspect of his brain research, and biological research in general, was to look at things in all their dimensionality. This very simple, and all too obvious proposition, has motivated him for many years. It seemed so appealingly obvious that I got myself rather entrapped in his intellectual web.

Its of considerable interest that within the last two years great progress has been made in 3-dimensional imaging, not only with respect to the reconstruction of pixel data but also in graphics technology where wholly realistic (and occasionally "more than realistic") models have been constructed. The application of these new computational capabilities to visualization research are quite remarkable. One of the more notable examples is the volumetric 3-D reconstruction of CT scans. It is likely that the next important contribution of computer science to biomedicine will be in this direction. In particular, 3-D mapping of the brain as well as molecular modeling will benefit the most. The clinical implications for this 3-D technology are very obvious and practical applications in clinical imaging are developing daily. The technological breakthrough here is the advent of parallel processors with huge memories, capable of up to gigaflop speeds and at prices, depending on size, as low as \$80,000.

A SEED OF DISSENT

Having rummaged around in the past and a bit in the future it is hard to escape the impression that most of what has happened was serendipitous. I reluctantly subscribed to this imperative although it has always made me uncomfortable. In writing here, to a large extent, serendipity is being justified since much of the neat stuff just described "happened by accident". It certainly wasn't planned by the N.I.H. or the U.S. Public Health Service. However, is such a monolithic research strategy in National or human interest? It is disturbing to observe that despite

a current annual N.I.H. budget of \$6 billion, we do not have a cure for cancer, AIDS, or any other significant chronic disease. Certainly there has been a general increase in our understanding of the biosystems that are involved, and yes, the survival rate for many forms of cancer have improved, but are we getting \$6 billion worth? If this were just an idle question, for which there were no alternatives, it might not merit attention. However, specific, goal-directed research, on any reasonable scale, has never, outside of the pharmaceutical industry, been attempted in the biomedical community. Serendipity is only one of a large number of possible strategies, and yet it has become so ingrained into our research and bureaucratic culture that it is largely unchallenged. Somehow the idea that scientific and/or technical progress depends entirely on accidental development is counter intuitive!

Recently my professional activities in R&D have been associated with the Department of Defense. Despite the recurrent climate of criticism for the magnitude and management of defense programs and expenditures, many of which do not equal the N.I.H. budget, much of the DoD modus operandi is goal oriented. The experience has convinced me that there are other highly effective strategies than those employed in biomedicine. This turns out to be a very complex set of issues, not only at broad philosophical levels, but also in terms of the specific ways that government institutions manage R&D. The easy excuse for raising this controversial issue here is the invitation to discuss the Planting of Seeds!

MEDICAL INFORMATICS:
A PERSONAL VIEW OF SOWING THE SEEDS

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Introduction

I am writing this paper as a personal and rather chatty account of some of the circumstances that led to a number of the research accomplishments of my career. If I were asked which of these accomplishments I feel are most well known today, I would mention four in particular. The first I would call the 'reasoning foundations of medical diagnosis', which is the title of the paper that appeared in Science that I wrote together with Dr. Lee B. Lusted in 1959 [1]. This paper has been called the 'initiating' paper in medical informatics. The purpose of the paper was to outline methods by means of which a computer might assist the physician in making a medical diagnosis. In it we propose the use of many mathematical methods which today are now included in the field of "artificial intelligence". In that paper we used methods of Boolean algebra or symbolic logic to help identify the disease diagnosis; we included the application of Bayes' formula for cases in which the probability of a correct diagnosis has to be estimated, and we also included the use of mathematical value theories for selecting the treatment. The paper itself stimulated great interest and what pleased me most was how much it stimulated other researchers to subsequently publish their views on a huge variety of methods and techniques for accomplishing computer aids to medical practice.

The second of my accomplishments which is generally known today is the development during 1973 of the first whole-body CT scanner, called the ACTA Scanner, which was put into routine clinical operation at Georgetown University Hospital in February of 1974 [2]. The design of the ACTA Scanner laid the foundation for modern CT scanners and also for many of the fundamental aspects of magnetic resonance imaging. The ACTA Scanner first used the convolution algorithm for

image reconstruction in computerized tomography, first used a digital image memory for driving a TV display which included color coding of the CT values, first incorporated a tilting gantry, and was first in many other innovations. The first ACTA Scanner built in my laboratories is now on permanent exhibit at the Smithsonian Institution's National Museum of American History in Washington, D.C.

My third accomplishment was the early development in 1962 of computerized medical imaging and pattern recognition [3]. Automatic computerized aids to chromosome analysis was the initial problem chosen, and along the way we developed a film scanner called FIDAC that interfaced to an IBM 7090 computer, we developed the method of syntax-directed pattern recognition, we developed the hardware and software for the interactive editing of chromosome images prior to the advent of modern digital image memories, and we developed a rapid television scanner for input to an IBM 360/44 computer, and many other innovations. Initially, I worked with Professor Frank H. Ruddle, and then with Dr. Herbert A. Lubs. We actively assisted in helping to establish medical imaging research groups in England, in Canada, at the Lawrence Livermore Laboratories, and at the University of Florida, by constructing FIDAC instruments for them and giving them our software, and we believe our research papers have stimulated many scientists to work in the computerized imaging field. In 1968 I established the scientific journal Pattern Recognition, which quickly became a standard source of articles in the general field, even up to the present time.

Finally, the Protein Identification Resource (PIR) (formerly the Atlas of Protein Sequence) is widely known as the world's known primary comprehensive knowledge base for protein sequences [4]. Although I was the first principal investigator in 1962 of the NIH grant that led to the initial Atlas [5], and I am presently principal investigator of the Protein Identification Resource [6], the Atlas and the PIR were mainly developed by my late colleague and associate Dr. Margaret O. Dayhoff [7]. However, I list this as one of my important accomplishments, because I like to believe that my encouragement and occasional management of the Resource helps to insure that it will continue to

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grow as a primary biomedical resource for scientists engaged in advancing biomedical science from a molecular genetic viewpoint.

On the other hand, if I was asked what other scientific accomplishments I have made in the past that in fact I wish were more well known today, I would have a rather long list. The list would first include some of the books that I have authored, namely the handbook Computers in Biology and Medicine [8], which was published in 1965 to assist biomedical researchers in using computers, the engineering text Digital Computer and Control Engineering [9], published in 1960, which was the first textbook for engineers written about how to build a digital computer, and Programming and Utilizing Digital Computers [10], published in 1962, which included what I believe is the first chapter written in a book on artificial intelligence, namely the chapter on "Programming to Achieve Intelligence".

With respect to my continued work in medical diagnosis, I wish that some of my analytical results in symptom disease relationships and further analysis of Bayesian probabilities were more well known [11]. Actually, many of these results were based on my early work in the 1950's on computational methods on Boolean algebra [12] and the formulation of antecedence and consequence problems in Boolean algebra [13]. These methods were originally developed for use in the logical design of digital circuits [14] but were then applied to the medical problems [15] and also to operations research intelligence problems [16]. Although the logical circuit design methods are well known to engineers, they are, unfortunately, not associated with my name as originator but have blended into general engineering knowledge.

Of course, since we built the first whole-body CT scanner, we were able to write the first articles on three-dimensional reconstruction from sequential CT sections [17], on the determination of bone calcium concentration from CT scans [18], on the use of CT scans for planning radiation therapy [19], and many more [20]. Again, although these results are now well known, unfortunately the fact that the first papers on such applications of CT were developed in my laboratories is not well known.

In medical imaging as well, I have a number of accomplishments which are well known but are not now associated with me. In particular, I initiated the field of syntax-directed pattern recognition [21]. I developed in 1971 and received a patent for the concept of the special-purpose image array processor which I called TEXAC (later sold as the DeAnza IP5000) [22]. In medical imaging we developed the first methods for analyzing the three-dimensional structure of Golgi-stained neurons [23], and we helped stimulate the medical imaging field by publishing a dozen applications of computer analysis of medical images in such areas as automated chest x-ray measurements, pap smear analysis, differential white blood cell recognition and counting, automated lung alveolar section measurements, analysis of synapsis in

electron micrographs, and many more [24].

Finally, I have often wished that some of our other instrumentation developments were more well known, such as the CENOG (Computerized Electro Neuro Ophthalmograph) [25] which computerizes, quantitates, and integrates in a single instrument almost all ocular-motor and vestibular ocular-motor tests, the GUDFU (Georgetown University Digital Fluorescopy Unit) [26] which was one of the first digital subtraction angiography units that had capabilities still not incorporated in commercial units, and the AGA (Automated Genetic Analyzer) [27] which uses a robot arm to automate the Southern blot experiment for detecting genetic defects on a molecular level and promises to bring this capability into the hospital clinical laboratory. Also, more recently we have developed a modern, stand-alone automated chromosome analysis machine called the Metachrome [28].

In addition, I should not forget that in 1965 we wrote the first computer programs for analyzing the optical system of the eye [29], and that the first research accomplishment of my career was the development in 1952 of dental force analysis, which explains why human teeth have cusps and has important applications to the construction of complete dentures and other dental procedures [30].

My Early Years

But getting back to the story of my career, my serious scientific education started in the 1943 at the Physics Department at Columbia University where I went to college. In those days undergraduate physics included only two semesters of college physics, and undergraduate mathematics ended with three semesters of calculus; almost all other physics and math courses were given as graduate studies. Taking a few graduate physics courses convinced me I should take more math, which I did, but after taking many graduate math courses, I discovered that this math was not the mathematics of physics. So, after a stint in Columbia Engineering School, I went back to graduate physics. I was trying to "find myself", about 20 years ahead of the kids of the 1960s. But things only went from bad to worse when my parents convinced me that a career in physics was not feasible, because in those days (it's hard to believe this now) everyone knew that physicists were either independently wealthy gentlemen or starving dedicated scientists, and I was neither. The solution was to send me to dental school (there are a few dentists in my family) with the promise that I could continue my physics as a well-to-do dentist. So off to NYU Dental School I went, from 8:30 a.m. to 5:00 p.m. each day, after which I took the subway up to Columbia to take physics courses from 6:00 p.m. to 10:00 p.m. each evening. Thus, I was studying gross anatomy, histology, pathology, microbiology, physiology, etc. at the same time as atomic physics, nuclear physics, analytical dynamics, quantum mechanics, etc. I started out each morning carrying 12 sandwiches, and the bag was

empty each evening. Professor Rabi would poke fun at me saying I was the only physics student he knew who could pull a tooth. I was working hard at "finding myself". After graduating Dental School in 1948, I continued and practically exhausted all the graduate physics and math courses at Columbia by 1950, when I picked up a Master's degree. But Columbia physics was truly exciting; I had such famous teachers as I. I. Rabi, E. Fermi, H. A. Bethe, W. Lamb, H. Yukawa, J. A. Wheeler, and others. I learned years later that they were all at Columbia because of the 'Manhattan Project' (i.e. the Atomic Bomb project).

Suddenly, in 1950, because I was a dentist, I found myself in the Army. It seems that the North Koreans decided to go South, and I was given the choice of volunteering as a 1st Lieutenant or being drafted as a Private. As a 1st Lt. I was sent to medical field service school, and after that, because I was a physicist, I was stationed at the National Bureau of Standards in Washington, D.C. to work in the Dental Research Section there.

Computer Science

That was a stroke of good luck; I began to really "find myself". The day I arrived at NBS I found out about the SEAC [31] (Standard Eastern Automatic Computer), the world's first high-speed electronic digital computer in which the programs were stored digitally in the computer's memory. (The ENIAC had a plug board wired program; I believe that Wilks' computer in England began to operate two weeks after SEAC, and the UNIVAC was still not operational.) I had previously realized that although, conceptually, physics equations could be written to describe any biomedical phenomenon, such equations would be so complex that they could not feasibly be solved in closed form. Thus, the SEAC was my panacea, because the equations would become tractable to numerical methods of solutions. Or so I truly believed at the time! That was to be my field, application of computers to biomedical problems.

Unfortunately, the first problem was to learn about SEAC, and I enthusiastically took up the task. The engineers who designed SEAC were very friendly and they unhesitatingly taught me all about the SEAC's engineering design. I carried out my first research project, applying SEAC to my dental force analysis. In 1953, I was out of the Army, and I took a job in the computer division at NBS to continue learning about digital computers. They had just completed designing and building a second computer called DYSEAC, and were applying it to an experimental computerized air-controller system using National Airport radar. My job was to do the programming so that an operator using a joy stick cursor could interactively enable the computer to track all aircraft in the area. That was undoubtedly the first real-time, interactive graphics program that also incorporated time-sharing for multiple terminals. And it was written in hexadecimal machine code, because assembly languages and high level languages like FORTRAN had not yet been developed! Although the project was successful,

the air controller system was not well written up in the scientific literature by the staff at NBS.

In studying the engineering of digital computers, I came across the problem of the systematic design of digital logic circuits, which was not well worked out at the time. To solve this problem I developed new mathematical computational methods in symbolic logic (or Boolean algebra). These methods were just as applicable to military intelligence problems as they were to digital logic design, and so in 1954 I wrote an article for the journal Operations Research on a "digital logic machine". Further developments of mine included the general formulation of Boolean algebraic computational problems in terms of solving for antecedences and consequences of given Boolean functions, the development of methods in multivalued Boolean logics, and in the application of Boolean matrices to solve Boolean equations. This area has subsequently become a mathematical field in its own right.

At that point a series of incidences occurred which finally brought me back to my original intention, computers applied to medicine. Eisenhower was President, Weeks was Secretary of Commerce, and Astin was Director of NBS, when the Post Office Department asked NBS to evaluate a so-called battery additive (which I believe was Coca Cola) that was sent through the mails. The Bureau said the additive didn't work, Weeks said the Bureau didn't understand the 'play of the marketplace', Astin (who lived on Battery Lane) was put on the hot seat and the budget of NBS was slashed, and Eisenhower couldn't care less. The computer division was the first to go, and IBM hired the computer design group 'en masse', and the rest of the engineers were dispersed around the country. I eventually was offered a job by George Shortly, a brilliant physicist who was editor of Operations Research, because he liked my paper on the digital logic machine. The job was at the Operations Research Office, a part of Johns Hopkins University. There I continued my development in computational methods and logic. One day I met George Gamow; he introduced me to the DNA problem, made me a member of his amino acid tie club (there were about 20 members, and I think I was lysine), and encouraged me to apply some of my methods to that problem.

Next, in 1956 I took another operations research job at GWU, but within a few months the director of this group, Dr. Glen Camp, told the Navy Department that they should revitalize sailing ships, and so he lost his contract. But GWU was loyal to its employees, and to relocate me they arranged an interview with Professor Earnest Frank, Chairman of the Electrical Engineering Department of the Engineering School. This was my second lucky stroke, because Earnest Frank had developed the theory of vector electrocardiology (at the same time and independently of Otto Schmidt), and therefore he welcomed with open arms an engineer who was interested in biology and medicine, and incidentally also was knowledgeable in the new hot engineering field of digital computer design.

I immediately arranged one of the first digital computer engineering courses in the country in 1957, and that led to my writing of the first textbook for engineers on how to design a digital computer, namely Digital Computer and Control Engineering, published by McGraw-Hill in 1960.

Medical Informatics

My friends, knowing of my combined interest in engineering and biomedical research, introduced me to Dr. Lee Lusted, who at the time was at the National Institutes of Health, and was an engineer and a physician. Our common interests immediately became apparent and resulted in our work on the reasoning foundations of medical diagnosis. The idea of using computers to assist in medicine had, of course, been discussed from time to time by many people, but a specific idea of how to go about it had not been published. My attempts in the area were actually first made a few years earlier while I was at the Bureau of Standards where I put together a deck of the McBee key sort cards (the cards with the holes around the margins) for diseases of the tongue. Each card was a disease, and the holes represented symptoms, and the symptoms related to the disease of the card were punched out to the card margin. Then, if needles were pushed through the edge holes of the deck of cards corresponding to a selection of symptoms, the cards that dropped would be only those corresponding to diseases having these symptoms. I even made a little device for facilitating the shaking and dropping of the cards, and as I carried this deck and my device around the halls of NBS, it didn't take the physicists more than a fraction of a second to say to me, "Oh, you're going to automate medical diagnosis, huh?" Of course, the cards did not truly carry out the logic that was required, and of course no probabilities are involved. But this work led Dr. Lusted and I to our first research accomplishment in medical informatics in 1959.

In our work we proposed the use of Boolean algebra or symbolic logic to eliminate disease possibilities based on the patient's symptom profile. We worked out methods for determining the most effective combination of medical tests for making the diagnosis, using the logical concepts of redundant and independent symptoms for the situation at hand. Where a number of disease diagnosis possibilities still occur, we proposed the use of conditional probabilities and Bayes' formula to determine the probability with which the patient may have the alternative diseases. Our theory demonstrates the importance of not considering symptoms as independent even if the assumption of independent symptoms simplifies the computations. The use of conditional probabilities in the diagnostic process leads naturally to the use of value theory in the choice of treatment. We proposed the use of transition probabilities (i.e. the probability that a change in the state of health of the patient will occur) in the choice of treatment, as well as the use of transition values in such a decision. We felt that our quantitative theoretical formulations help the analysis of the diagnosis-treatment problem, and

point to directions that should be taken in the collection of statistical data. Also our methods have direct application to the judicious evaluation between two or more possible new treatments, and so forth. Dr. Lusted and I wrote many papers on these concepts, and I also included these in my book, Use of Computers in Biology and Medicine.

But I'm getting a little ahead of myself again. Back in 1957, and with the recommendation of Dr. Lusted, the National Academy of Sciences-National Research Council asked me to do a survey of the potential of the use of computers in biology and medicine. This survey was supported by the Air Force and was to result not only in a survey [32] but also in a handbook to assist biomedical researchers in their use of computers.

The survey that I carried out for the NAS-NRC gave me the unique opportunity to talk with many biomedical researchers throughout the country about the potential of computer applications in biomedical research. These were incorporated in some detail in the handbook Use of Computers in Biology and Medicine. However, the Dean of the Engineering School at GWU at the time was unwilling to put significant resources into such applications of computers, and therefore I was unable to initiate my own research in this field. But at the NAS-NRC I was advised that I might start an independent nonprofit organization devoted exclusively to computers in biology and medicine, and indeed we did that. The NAS-NRC kindly gave us office space, loaned us office furniture and equipment, and the National Biomedical Research Foundation was established in June of 1960.

Medical Imaging

One of the first projects I initiated at NBRF was to build a film scanner and digitizer for inputting images into a digital computer. It consisted of focusing a flying spot from a cathode ray tube raster scan through the black and white image on the film, then detecting the transmitted light with a photomultiplier tube, and finally digitizing the electronic signal into four bits representing up to 16 grey level values. The binary stream was interfaced directly into a computer. At first we adapted a 16mm camera for the purpose, and later in 1963 a 35mm reflex camera was used. The first system was built onto a laboratory cart, but later scanners consisted of two racks of electronic equipment. The scanner, called FIDAC, had a 2000 x 2000 pixel resolution, and inputted the grey level data at the maximum rate of which the computer was capable. If unexposed film were used, the FIDAC could produce grey level images. It must be realized that digital electronic technology in 1960 was not what it is today; all circuits had to be designed, built, and tested; there were no integrated circuit chips, and individual transistors were used. The computers of that time had no general interface boards; the FIDAC was wired directly into the computer.

And, of course, NBRF could not afford a

computer, or even afford to purchase time on someone else's computer. But I had faith that if we built the scanner, someone would give us free time on their computer. And our white-knight turned out to be a combination of IBM and Westinghouse. Looking back now, it was incredible that IBM paid for computer time on their 7090 computer at the Baltimore Westinghouse plant, and that Westinghouse let us wire our scanner directly into their computer while they were printing their payroll checks and calculating sensitive military data. Our first attempt at connecting the 7090 resulted in scrambled data, but IBM flew in a team of eight expert engineers to find that they had given us some connector pin numbers backwards. Eventually, and at no charge, IBM loaned us three top programmers who worked with us for several years, and the Goddard Space Flight Center gave us free computer time on their collection of IBM 7090 and later IBM 7094 computers. The imaging work was first supported by the Joseph P. Kennedy Jr. Foundation, and later by grants from NIH. Initially we worked on automated chromosome analysis together with Dr. Barbara Migeon of Johns Hopkins University; later we cooperated with Professor Frank H. Ruddle of Yale University on the chromosome problem.

In 1964 I was invited by the Medical Research Council of England to a conference in Oxford, to discuss our imaging hardware and software developments. They purchased a FIDAC and our programs, and then later they hired Dr. Denis Rutovitz to head their automatic chromosome analysis group. The FIDAC was flown to England and we crated its parts in wooden boxes carefully measured to fit through the cargo door of the aircraft. But at first the airline men could not get the boxes into the plane, and I remember standing in the middle of the Dulles Airport runway to show the men how to turn the boxes so they would fit through the door onto the plane.

I invented syntax-directed pattern recognition for recognizing objects such as chromosomes in any orientation, and the BUGSYS programming language to implement the syntax techniques. BUGSYS consists of a collection of conceptual pointers (bugs) that are programmed to move over the image to determine boundaries, areas, orientations, curvatures, etc. involved in the pattern recognition and measurement process. Using these methods we developed programs to separate touching objects, separate overlapping chromosomes, etc. We were able to successfully classify chromosomes into the classical A-G groupings just in time for the advent of banding patterns. So we continued on and studied Giemsa banding profiles, and finally were able to discriminate individual chromosomes according to the Paris convention with 96% accuracy. We also applied our scanner and computer imaging methods to the first three-dimensional analysis of Golgi stained neurons from sequential microtome sections of the neurons. We had an NIH grant awarded for this purpose, and obtained our neuron material from Dr. Van der Loos, of Johns Hopkins University, and Dr. Alden Dudley of NIH.

In 1968 NBRF obtained a grant from the John

A. Hartford Foundation for the down payment on an IBM 360/44 computer. We also applied for a grant from the NIH to support the computer, but for some reason the award was delayed. Meanwhile, with no signed sales agreement, our trusting friends at IBM actually delivered and installed the computer. Finally, the NIH grant was awarded, and, being the honest fellows we were, we signed a sales agreement and paid the quarter of a million dollars for the computer. The computer was well used. We designed and built an interactive graphics system for our pattern recognition laboratory in 1968, developed a computer-controlled microscope in 1969, and by 1971 we had completed a high-speed vidicon scanner that could input into the computer a raster of 672 x 450 (or over 300,000) pixels in one-third of a second, a speed that was orders of magnitudes faster than other scanners being developed at that time. At that time we were cooperating with Dr. Herbert Lubs, of Yale University, and later also with Dr. Paul Ing of the University of Colorado, on the chromosome analysis.

By 1970 it became clear that the field of computers in medicine was well accepted by academic institutions. It was suggested by both George Washington University and Georgetown University that NBRF became an affiliate. Even though between 1968-1970 I was back as a part-time professor in the GWU Engineering School, I felt that having our laboratories in the midst of the Georgetown Medical Center would be more advantageous. Therefore, at the invitation of Dr. John Rose, Dean of GU Medical School, NBRF affiliated with Georgetown, moved into an area in the newly completed Preclinical Science Building, and I became a Professor in the Physiology Department of the Medical and Dental Schools. The space we occupied (and still occupy today) was designed to be a computer center, and in the seventies architects always put them in the basement, and in our case, actually underground. There is a lawn above us, and we call our offices the "ivory dungeon". By late 1971 we had set up at Georgetown what was one of the most advanced computer image processing laboratories ever assembled at that time, containing unique equipment developed by us. The graphics interface, called MACDAC, used the early Tektronix 'write through' storage scope, since digital display memories were not yet generally available; the vidicon scanner, called VIDIAN, used a scan-converter tube to temporarily store an image for later input to a computer at slower than TV scan rates, for computers at that time could not accept information that fast; the computer-controlled motorized microscope stage we developed, called SPIDAC was very high speed and had a positional accuracy of one-and-a-quarter microns; we had developed a very high resolution drum scanner; and finally we had an improved FIDAC film scanner. All these interfaced directly into the IBM 360/44 computer.

Thus, by late 1971 we had used our imaging system to automatically recognize all chromosome spreads on a glass slide within one minute, and then to relocate them for operator review and interactive editing of touching and overlapping

chromosomes, and then to perform a karyotype based on the Giemsa banding patterns of the chromosomes. In addition we applied the system to the analysis of many other biomedical images.

Although we were very successful in our work on medical image processing, and had an approved NIH grant for our laboratories due to be renewed, disaster threatened in early 1973 when Nixon, who was President, impounded some of the NIH funding, and the grant was not paid. We also had another spate of bad luck. I had asked NIH for a contract to build a 'stand-alone' computerized chromosome analysis instrument to be based on a smaller computer than our IBM 360/44, but the contract was given to Jet Propulsion Lab. The review committee made a site visit to JPL but not to NBRF, and deduced that JPL had a 'better chance of developing a vidicon scanner' than NBRF, apparently not realizing that we at NBRF already had built a vidicon scanner and were already using it for chromosome analysis. But, as fate would have it, in retrospect, I have great difficulty in complaining about the Committee's decision.

In fact what I had thought was bad luck turned out to be another stroke of good luck, for it led directly to my development of the first whole body CT scanner! Administratively, we embarked on the development of the CT scanner, both to save Georgetown University some money and to help keep the NBRF bioengineering and imaging group alive. By February 1974 the CT scanner had been completed and both administrative goals fulfilled. Then, lo and behold, in May of 1974, NBRF received a check and the original grant award! It seems that someone went to court and unimpounded the impounded NIH funds, and our previously approved grant was paid one year late. Thus if the grant had been paid in 1973, or if we had received the contract, we would never have developed the first whole body CT scanner. And in the end we were awarded the grant anyway, and it turned out that in 1987, fourteen years later, we built the Metachrome instrument, a sophisticated stand-alone automatic chromosome analysis instrument that includes the high speed (within a few minutes) finding of chromosome spreads on a glass slide using present-day modern computer and electronic technology. But I am getting ahead of myself at this point.

The NIH grant that was finally awarded in 1974 was for medical imaging hardware and software. Based on our previous experience in image processing, the grant application proposed the building of a new and innovative type of image processor, which would consider whole pictures as 'arguments', and process all the pixels in the argument pictures within the frame-grabbing time of a TV camera, namely within one-thirtieth of a second. Thus, for instance, if two pictures were to be added, pixel by pixel, then the value of each pixel of the resulting picture would be the sum of the values of the corresponding pixels in the argument pictures. Conditional operations were also included, where for example, a pixel in the resulting picture would be replaced only if the corresponding pixel in the first argument was greater than that in

the second argument, etc. We called this whole image array processor TEXAC for Texture Analysis Computer. Its great value lies in the extreme speed with which the whole image operations can be performed, and we have applied it to the chromosome analysis, muscle fiber analysis, platelet aggregation studies, the tracking of vacuoles in nerve fibers, etc. I received a patent in 1978. The original electronic implementation proposed in the grant application involved sets of three image-converter tubes for each image memory, but by the time it was actually fabricated in 1976, digital memories became readily available. The contract NBRF gave DeAnza Systems to fabricate the TEXAC specified that our design was to be held confidential, but DeAnza, seeing a good thing, made it a product, namely the IP5000 and subsequent machines. By the time NBRF hired some lawyers, DeAnza was bought by Gould Inc., a very large electronic firm, and the U.S. Government sided with Gould; it is ironic that recently, according to the New York Times, Gould Inc. has been accused of overcharging the U.S. Government for image processing equipment and has been prevented from bidding on Government contracts.

In any event, I believe it is fair to say that the concept of whole picture image array processors, originated at NBRF, has had a great influence in the field of image processing, and, in fact, at an IEEE meeting in Washington, D.C. in 1977, a report on, and demonstration of TEXAC was given the "best paper" award.

Computerized Tomography

As I mentioned above, we worked on CT because in early 1973 all our other bioengineering funding suddenly disappeared. Hearing about our problem, Dr. John Rose, Dean of the Medical School, told me that Dr. Luessenhop, Chief of Neurosurgery, was about to spend \$500,000 for some type of scanner, and since we made 'scanners' perhaps we could make it cheaper and save the University money and support our group as well. I checked with Dr. Luessenhop to find he was planning to purchase Hounsfield's computerized tomographic head scanner, announced by EMI. The idea of computerized tomography was well known to me; in the 1960's, Kuhl at the University of Pennsylvania had constructed an instrument to perform computerized transverse axial tomography with signals emanating from the body injected with radioactive material; Tretiak had scanned x-rays of a femur bone taken at different angles and reconstructed a cross-section in 1971; and in the early 1960's Cormack had completed an experiment demonstrating the accuracy of the reconstructed absorption coefficients. Thus, looking at the EMI brochure, I couldn't see why their proposed scanner required scanning through a water bath which limited its use only to the upper part of the head. Also, the cross-sectional images shown in a book by Takahashi on non-computerized transverse axial tomography really made me feel that a whole body computerized transverse axial tomograph could be feasibly developed. For if such reasonable, albeit fuzzy, cross-sections could be obtained without a computer, then the

use of a computer, as shown by Cormack, should result in clear sharp images. So I told the Dean that I could develop a whole body CT scanner, not just limited for use on the head, and for half the cost. The University said that NBRF should do the development, and if it worked, the University would pay for it. I called it the ACTA Scanner (for Automatic Computerized Transverse Axial Scanner). We started in June of 1973 and it was in routine clinical operation in February of 1974.

The development of the ACTA-Scanner was perhaps the ultimate exercise in the cross-disciplinary approach, involving the design of mechanical equipment of considerable complexity, the handling of high voltage x-ray equipment that was moving, the development of electro-optical mechanisms of a non-trivial nature, the sophisticated handling of real-time computer-input data, the writing of highly detailed and efficient numerical-analysis computer programs, and the utilization of advanced display techniques. And these had to be coupled with a system design formulated for the medical needs of the physician, involving radiological methods, neurosurgical requirements, concepts in pathology and anatomical knowledge. The vocabulary required for a detailed understanding of the practical medical needs and potentialities of such a system had to be understood by the engineer and translated into specific component design utilizing the current engineering "state of the art". Gross anatomy, mechanical design, oncology, theory of gears and cams, elements of radiology, electro-optical methods, radiation physics, digital computer engineering, pulmonary physiology, mathematical methods of Fourier analysis, osteology, assembly-language programming and many more were all intimately involved in our cross-disciplinary development.

It was uncanny; almost all my scientific studies and much of my previous scientific experience, were required for the development. The diversity of my background now made sense; I sometimes felt as if I had somehow been guided for this purpose. I had taken a course in mechanical design during my short stint in Columbia University's Engineering School, which I needed to be able to design the mechanical gantry; from my study of gross anatomy I knew that the gantry should be tiltable to clearly see the spinal disks; I was familiar with ordinary x-ray tomography because when I was in the NBS Dental Research Section, they were perfecting the Panorex, an x-ray tomograph that imaged all the teeth on one film by rotating the x-ray tube around the patient's head; I had pioneered in computerized image processing and display; and I had taught courses in numerical analysis at the GWU Engineering School.

The first step in our work was to simulate the system on our own computer, an IBM 360/44. After considerable experimentation with various approaches, we chose the one that presented the results immediately after the mechanical scan was completed, and that required no "water bag", so that any place on the whole body could be

scanned, and so that the diagnostician could see the results from the patient immediately, thereby being able to make another scan, or give contrast medium, etc. while the patient was still on the scanning bed. In general, the picture-reconstruction problem turned out to be primarily in numerical analysis and assembly-language programming. We chose as our algorithm a convolution, and initially used the formulation of Ramachandran and Lakshminarayanan published in the Proceedings of the U.S. Academy of Sciences in 1971. (Many years later I found out that Hounsfield needed the water bath because he used the wrong algorithm; all modern CT scanners use the convolution algorithm as I originally did.) Then I made a balsa wood model of my concept to impress my staff with the fact that we were actually going to make this "far out" machine. In this way we could visualize the entire prototype scanner while its individual components were being designed.

I knew that a successful medical instrument must present the physician with immediate information in the form that can most easily be assimilated, and I emphasized the result-display aspect of the design. Towards this end, a color-coded key method was conceived so that the physician could obtain numerical results at a glance by observing colors on the picture corresponding to numerical ranges. The various anatomical structures, as distinguished by differing relative absorption coefficients are displayed as colors on a color TV screen. By looking at the screen, the physician can at once comprehend the anatomical pictorial pattern, as in studying ordinary x-ray plates, and gain numerical data as well by means of the color codes. The use of the TV display also has the advantage that the picture appears constantly (whereas in Hounsfield's head scanner, the picture was swept out only once each 10 seconds and a Polaroid time exposure had to be made). Since radiologists are remarkably adept at observing substantial detail in black-and-white x-ray images, a black-and-white TV was also included. This high resolution TV display, based on a digital image memory, was a 'first' in medicine (and in addition, presented four times the resolution of the Hounsfield machine).

The working environment and the attitudes of colleagues probably have as much to do with the success of such a project as does technical skill. There is no doubt that those of my medical colleagues who encouraged me the most may have had the least idea of the extreme engineering sophistication required and the great difficulties that had to be overcome. The sustained and unrelenting encouragement we received was perhaps our greatest asset, for it enabled us to carry out a dedicated effort over a prolonged period of time. However, we cannot say that we did not have detractors. There were those who predicted doom, those who insisted the project required 10 times the financial effort and 6 times as long for the development, and those who tried to erode our enthusiasm. Of course, after we had been successful they said that the accomplishment was minimal, and anyone could have done it, and something far better is

just about to be done by somebody else!

Our first scan was made of a navel orange placed inside a human skull, all of which was put into a plastic bowl filled with water. The skull was only half immersed in water, and the orange floated on the surface of the water inside the skull. The ACTA Scanner was making a vertical cross-section of the bowl, and we waited anxiously as the scanner completed its mechanical movement, and we were excited to see the picture instantly flash onto the TV screen. There before our eyes the water, the skull, and the orange were all clearly delineated. Even the difference between the more dense outside orange layer of the peel could be distinguished from the inner white pulpy part of the peel, and the plastic of the thin bowl could be seen.

Murphy's law, that "if anything can go wrong, it will", was always at work. Take one of our first human patients for example. He was supposed to have a middle fossa brain tumor. The ACTA Scanner showed a large edematous mass in the right frontal lobe and no ventricles! So the neuro-surgeon said, "Don't feel so bad, it's only your first scan. Keep on plugging". But the next morning, after surgery, we got an excited phone call: "Guess what! The patient had severe edema through the right frontal lobe!" Then there was our first case of enlarged ventricles: posteriorly there were dense patches in the ventricles, and I couldn't figure out how that kind of noise could get in there. But after one glance the neuroradiologist said excitedly, "Look at those great choroid plexuses!" So I went home to review neuroanatomy from my 25-year-old textbook.

The most memorable of the earlier cases was the lung scan of an oleothorax. This condition is caused by the injection of oil into the lung of a tubercular patient, a treatment used about 50 years ago; the body forms a capsule around the oil. The ACTA scan of the patient showed the low density oil still in the patient's lung, floating on top of the more dense serous fluid, all of which was inside of an even more dense fibrous-tissue capsule. In addition, the heart cross-section showed the atrial chambers, filled with blood of the same density as the serous fluids of the oleothorax, and heart muscle of the same density as the fibrous tissue capsule. All on a living, breathing patient!

After the first series of successful ACTA scans, bottles of champagne suddenly materialized out of our neurosurgeon's desk drawer. The Chairman of the Physiology Department and the Dean of the Medical School, the Medical Director and the Administrator of the Hospital, the Chancellor of the Medical Center, and all our friends showed up, and a picture of our group was taken as I held a gigantic wrench used to put the machine together. Amid the loud shoutss of joy could be heard muted sighs of relief.

But in fact there was no letting up, and our sighs of relief only lasted a fleeting instant. All the x-ray manufacturers visited Georgetown to see the ACTA, including G.E., CGR, Picker,

Phillips, Siemens, and Ohio Nuclear (later known as Technicare) to name a few. Even Hounsfield and EMI representatives visited me several times. We offered rights to the ACTA in return for long-term research support, but the medical x-ray companies showed no interest; rather their interest seemed to be to examine the ACTA so they could return to their factories to copy it. The worst case was Ohio Nuclear: they came out with a close copy of the ACTA in late 1975. At the same time, chiefs of radiology departments from universities and hospitals around the country also came to visit, and a group of leading radiologists requested that we build each of them an ACTA Scanner. So, with the acquiescence of both the NBRF and GU, we started a for-profit business, called DISCO (Digital Information Science Corporation) and began to manufacture ACTA Scanners with the hope of either using the profits to support our research or selling DISCO in return for research support. In September 1975 Pfizer Inc. established Pfizer Medical Systems and took over the ACTA Scanner in return for close to ten years of research support.

My Recent Years

My recent years have been mainly devoted to applying modern computer, electronic, and imaging methods to medical problems. There have been dramatic changes in computer hardware and software, and the computer revolution is still ongoing. Large-scale integrated circuits are becoming pervasive in electronic engineering, and the nature of electronic design is being rapidly transformed. The practice of medicine and surgery, in combination with the new technologies is being transformed and medical and surgical miracles are becoming commonplace.

Genetic engineering is already showing results, and scientists are seriously considering the sequencing of the entire human genome. But the functional result of a gene is the protein that results. The Protein Identification Resource contains the world's main database of such protein sequences. In 1978 NBRF donated its IBM 360/44 to the University of the District of Columbia, and purchased a VAX 11/780. The VAX holds the protein sequence database, and has been a great work-horse for the past ten years. Scientists from all over the world can gain telephone access to the database. In addition NBRF provides magnetic tapes of the database. Any scientist working with what is believed to be a new protein should check with the PIR. In our own work evolutionary trees are developed from protein sequence alignments, and important relationships between proteins have been discovered. I believe that the directions for the future be with the PIR.

Usually the people involved in the inception of a new field can only barely envision its eventual impact on society and science. I recall the beginnings of the computer field in the early 1950's, in which I was fortunate to play a part. Few appreciated at the time the extent of the pervasiveness which the computer was destined for in modern society. Even in the early sixties, my work with the application of computers in

medicine was considered as "pioneering". Nevertheless, there is a certain delight, indeed thrill, in being part of that whole new development in science and technology. I certainly did not foresee at the time I wrote the 'Reasoning Foundations' paper with Lee Lusted how large and important the field of medical informatics would become. The field of computerized tomography was imbued with this same excitement. It is heartening to see how pervasive CT is in medicine, and to see the great influence my first whole body CT scanner had on the industry. Even the Magnetic Resonance machines use features first incorporated in the ACTA Scanner. Now the future lies in genetic engineering, in working with the molecular basis of human disease. And computer technology and pattern recognition are intimately involved. I certainly am looking forward to witnessing the great new developments that undoubtedly lie ahead.

Acknowledgements

Over the years the NBRF staff did not change much, and there were many long-term engineers and scientists that made the research accomplishments possible. James B. Wilson, Louis S. Rotolo, and Margaret O. Dayhoff were with me the longest. Mr. Wilson and Mr. Rotolo are engineers and worked on the software and hardware of the imaging developments, the ACTA Scanner, the TEXAC and other instrumentation. Dr. Margaret Dayhoff developed the Atlas of Protein Sequences. Mr. Thomas Golab was and still is chief electronics engineer and worked on all the image processing developments, and on the ACTA Scanner. Dr. Hon K. Huang, Mr. Menfai Shiu, and Dr. George C. Cheng developed software for image processing, and Dr. Huang and Mr. Shiu wrote programs for special applications of the ACTA Scanner. Mrs. Marilyn Belson and Dr. Rosalie Dunn carried out automated chromosome applications.

Dr. Winona Barker and Dr. Lois Hunt have been intimately associated with the Atlas of Protein Sequences and are the principal scientists of the PIR. Dr. Barker is Co-Principal Investigator with me of the NIH research resources grant for the PIR.

Without the dedication and loyalty of these individuals and the work of a number of more transient associates, the research carried out by the Foundation could not have been accomplished.

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HISTORY OF THE DEVELOPMENT OF MEDICAL INFORMATION SYSTEMS AT THE
LABORATORY OF COMPUTER SCIENCE AT MASSACHUSETTS GENERAL HOSPITAL

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The reconstruction of history is always a difficult task. The important decisions, the critical issues never seem to be adequately documented and cannot easily be recalled. It is difficult enough in affairs of national importance to try to establish "who knew what, and when did he know it?" In considering the history of the activities of the Laboratory of Computer Science at Massachusetts General Hospital, I have found it equally difficult to try to establish: "what did we do, and why did we do it?"

I have little confidence in my judgment as to what were the important contributions of the Laboratory of Computer Science in the first decade of its existence, and even less confidence in my ability to recall and to interpret appropriately the contributions of a host of individuals who participated in the effort.

The only option seems to be to frame this presentation as a series of flash-backs consisting mostly of hazy memories of incidents and selected extracts from grant requests and progress reports. I do not pretend that these flash-backs are either a valid scientific quest or a valid historical review, and I fully appreciate that these memories are greatly colored by the events and the activities that have happened since that time.

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Two observations, however, seem uniquely important. Claude Bernard wrote: "Art is I; Science is We." I cannot emphasize too strongly this statement in reflecting over the history of the Laboratory of Computer Science which it has been my privilege to lead for almost twenty-five years. I have been enormously fortunate in having had the opportunity to work with a large number of enormously creative, imaginative, and effective colleagues who have played a major role in the contributions we have made in the past twenty years. No presentation would be complete and accurate without giving recognition to these individuals. I have often felt that my primary responsibility was to recruit good colleagues, and then try to provide the environment where they could be optimally productive.

There are too many people to name individually in this short presentation, but I will identify some of the key individuals in relation to specific projects. I know that I will fail to recognize many individuals who have made important contributions; this failure haunts me in my writing of an historical account of the Laboratory.

The second observation I would offer is that much of what is accomplished in life and in science seems in large part to be dominated by luck, by the accident of being in the right place at the right time, with the right resources, the right funding, the right opportunities. I believe this to be true in much of what we have accomplished at the Laboratory. I feel most fortunate that thirty years ago, due to a chance association of living together with a group of MIT electrical engineering graduate students, I became acquainted with computer technology and became captivated by it as an idle recreation. I still live in fear that someday it will be discovered that I am getting paid for doing my hobby, and that I will have to get a real job.

Preparing this manuscript has been somewhat of a revelation and somewhat distressing. Technology has developed at a fantastic rate and yet progress in implementation has been laborious and slow. I found it interesting and somewhat entertaining to read two paragraphs I wrote in reviewing this field for the New England of Medicine [1] almost twenty years ago:

"Early interest in bringing the revolution in computer technology to bear on medical practice was plagued with over enthusiasm, naivete and unrealistic expectations. The use of computers would, it was held, allow rapid and accurate collection and retrieval of all clinical information, perform automatic diagnosis, collect, monitor and analyze a variety of physiological signals, perform and interpret all laboratory tests immediately, and replace the telephone and the medical record by fulfilling their functions. In fact, however, attempts to apply computer technology to medicine have had only limited success, with numerous failures. The growing pains encountered in applying computer technology are not unique to medicine; the same types of experiences have been realized in all other areas of computer application. Indeed, one of the benefits of the computer revolution is that it stimulates and requires an intensity of thinking, a level of sophistication and a strictness of semantic behavior that are needed badly in the development of improved methods of delivering health care."

"The initial wave of optimism and enthusiasm generated by beguiling promises of an immediately available total hospital computer system has passed. Now, efforts are directed toward the painful, slow evolutionary process of developing and implementing modules or building blocks for individual functions. There is now a keen appreciation of the wide gap separating a demonstration project, however impressive, and an operational service system in daily use. Stringent reliability requirements and the difficulties attendant when nontechnical personnel (with a high turn-over rate) use a computer system on a round-the-clock bases have been two of the key limiting factors in HIS development. In addition, the very high initial costs often stagger hospital administrators; demonstration of cost-benefit savings is difficult. If the experience of other industries is repeated in hospitals, the use of computers in hospitals will not reduce total medical-care costs, but will lead to more effective use of the resources at hand and to improved patient care."

We are still in this painful, slow evolutionary process. We still face the reliability problems, the high initial costs. In reading these old articles I am impressed at how valid were our concerns twenty years ago, and how many of the issues we confronted then are still valid. For example, let me share several paragraphs of an article published in 1969 [2]:

"In papers devoted to the problems of hospital information systems, there is often a strong feeling of *deja vu*. For the past decade it has been repeatedly claimed that computers will be of enormous usefulness in patient care and in hospital practice. On innumerable occasions our old men have dreamed dreams and our young men have seen visions. Yet, when we critically examine what is actually being implemented in our hospitals, we are most impressed by the number of slow or halting starts, and the number of projects that have been abandoned or in which the objectives have been greatly watered down. The discrepancies between the visions and the realities are startling.

What is the cause of this state of underachievement when the need is so great, and the technology supposedly so powerful? This is a significant problem which merits considerable analysis. It is our thesis that a considerable portion of the difficulty involves the recognition and solution of the "interface" problems.

There are three important classes of interface problems: (1) the interface of the hospital with the development and implementation of a computer system; (2) the interface of the user with the computer terminals; and (3) the interface of the programmer with the computer system.

When one reviews the developmental projects which have been undertaken, there are several recurring themes. First, the magnitude of the problem is usually grossly underestimated and there is almost always inadequate concern for defining objectives and for planning. Hospital and medical staffs have had little prior experience in innovation in the area of information processing, and in many situations, the critical decisions are made by individuals in isolated departments who do not possess a broad view of the needs of the hospital..

Second, the computer industry has often displayed a considerable lack of understanding and of sophistication. On a number of occasions, the sales and promotional aspects of marketing hospital computer systems have been quite misleading and have led to false expectations.

Third, the hospitals have rarely made the depth of commitment of both administrative and professional staff that is required to develop and implement a viable system. This commitment must be in terms of years, in order to provide the exposure and experience necessary to copy with the complexity of the problems.

Fortunately, the illusionary concept of a total hospital information system is now disappearing, and there is a wider acceptance of the need for an evolutionary step-wise development over a period of years. Total systems suffer from limitations in terms of both definition and appropriate technology. We neither understand all the dimensions of the problem, nor do we have management structures or computer facilities that could support a total system. It now appears that the most logical course is the development of a series of modular systems, which will be interconnected and will evolve toward handling more and more of the information-processing aspects of patient care. It has been repeatedly demonstrated that the introduction of a radically new technology causes fundamental changes in the habit patterns and in the desires of the hospital staff. The objectives and procedures of the computer development must also evolve as we gain experience with computer systems in daily hospital operation."

My first flashback relates to my initial contact with the Hospital Computer Project contract held by MGH and a firm in Cambridge named Bolt Beranek and Newman (BBN). This contract, funded jointly by the National Institutes of Health and the American Hospital Association, began in 1962. The effort was directly related to the genius and imagination of one of the senior managers at BBN: Jordan Baruch. BBN was active in the early development of time-sharing computer systems, and had developed one of the first time-sharing systems on a PDP-1. Jordan had a vision of the useful impact that such a system would have on the information processing needs of a hospital, and persuaded the NIH to fund the effort. NIH insisted that there be a medical collaborator and MGH was drafted - with little knowledge or insight on the part of MGH as to what

was involved. There is an ancient letter in the files from the MGH director to the NIH stating that MGH would be glad to participate with the understanding that there would be no cost to MGH - after 25 years and the expenditure of many millions of dollars, this request seems somewhat lacking in foresight.

The time-sharing technology developed by BBN was at the cutting edge of computer science at that time, and the use of time-sharing at MGH was one of the first demonstrations of the potential power of remote access to a real-time, on-line data base. Jordan's early papers and reports are still fascinating in the range of the vision and the validity of many of the objectives. From the initial formulation, the system was conceived as being interactive and conversational in real time. The dialog was to have error-checking, to have on-line help, and to be branching in response to the particular set of entries given by the user. One of the most radical of the specifications was the plan to include "standing-orders" in the computer so that it could automatically detect and respond to specific data entries or to specific values of the data base. Jordan referred to this as "even-detection" or as an always active "demon" which continually monitored the data base. This is the first plan of which I am aware to take advantage of the computer system to use pre-formulated rules and is a model of what are now used extensively as "criterion-rules" or "on-line quality assurance".

The second flashback memory relates to how I initially became involved in the MGH medical information system developments. BBN had demonstrated impressive progress in developing computer technology, but there was little progress in hospital applications, and little involvement of the medical or nursing staff. I believe that the NIH site visit committee strongly suggested to MGH that it should take a more active role in the planning and management of the Hospital Computer Project, and that MGH should provide professional leadership. Following this advice, John Knowles (who was then General Director of the MGH) and Bob Ebert (Chief of Medicine) consulted with members of the computer student section and with NIH staff. It is my impression that two of you here today - Homer Warner and Bruce Waxman - were instrumental in my being recruited in 1964. This recruitment was facilitated by the circumstance that there was no one else they could identify who was interested in academic medicine and who had any experience in working with

computers. In several conversations with Knowles and Baruch, I became intrigued with their vision and with the potential to combine my hobby in computers with the practice of medicine. I am sure that none of us anticipated the problems we would encounter, the amount of time, effort and money that would be required, or the years of development that lay ahead.

My next flashback memory is of the first two years of the activities of the Laboratory of Computer Science from 1964-1966. Our initial efforts were focused on the development of an admission discharge census system, a laboratory reporting system, and a medications ordering system.

The computer system used in the initial time-sharing development was a PDP-1 computer with 16K of 18 bit words memory which supported 5 simultaneous users. This system was later upgraded to a PDP-1-D which had 48K of core memory and which was supposedly capable of supporting 64 simultaneous users.

There were no telephone line communication tariffs which could be used for data communication but we were able to obtain a tariff for direct current telegraph communication that had been established for communication along railroad tracks. The telephone company was generous in not requiring us to lay the railroad track between BBN in Cambridge and MGH in order to justify providing the 10 character/second DC communication. The terminals were standard Model 33 Teletypes which were placed on a few of the floors of MGH in 1964-1965.

All programs were written in assembler. Initially all programming was done only on the central console teletype. Programs creation and debugging would take weeks to months, and changes to a running program had to be strongly justified. One BBN report stated the criteria for revision to be: "what contribution will such revision make to the knowledge garnered by the project" and "is a new principle involved?"

Using this PDP system located 10 miles distant from MGH, we were able to provide what for those days were very impressive demonstrations of how a computer might be useful in processing medical information. We were, however, never able to do more than limited demonstrations, and were therefore never able to test any of the programs in actual operation. The major problems were unreliability of the computer system, slow speed of communication,

very limited functional capabilities, and user unfriendliness of the Teletype as an input instrument. In addition, because of the limitations of

programming in assembler language, any debugging or enhancements of the programs required weeks to months to accomplish.

Probably of greatest importance, it became obvious that there was an incompatibility in philosophy between the goals of BBN and the goals of the Laboratory. This difference can be illustrated by quoting one of the early BBN reports which stated: "For now we shall ignore questions of priority, time and cost. Let us work purely with definitions and ideas". In my judgment, these definitions and ideas which had been formulated by BBN were highly creative and had great promise. The hospital, however, marched to a different drummer in being more pragmatically oriented. The research project was rapidly losing credibility in that it could not meet the challenge of being used by regular hospital staff carrying out the normal daily tasks of patient care. Demonstration programs, however impressive, and promises for the future, however grandiose, could not substitute for the reality that all our computer programs could only function in the hothouse atmosphere of parallel operation for several days to several weeks and operated by our own research staff. There was no possibility for evaluating whether or not a hospital could be usefully served by such a system, and certainly no hope that we could persuade the hospital to spend its own money to implement such a system.

The next of these random flashbacks relates to the origin of MUMPS. At one of the first NIH project reviews, J.C. Shaw was one of the site visitors. Shaw is one of the early great pioneers of programming who worked at Rand Corporation with Newell and Simon. He had developed an interpretive language known as JOSS which he discussed over lunch at the site visit. One of the MIT students who was working with us on the project decided to implement the language on an MIT system over Christmas holidays. BBN management became

fascinated with the language and over the next two years implemented a number of versions of the language under the names of Telecomp and Stringcomp. These languages provided algebraic programming support and had only primitive string handling functions and no file handling capability.

At about this time, Jordan Baruch persuaded General Electric to enter the business of time-sharing computer support for the hospital industry. This new GE subsidiary, known as Medinet, had very ambitious goals - simultaneously to develop time-sharing hardware, a new language and a complete set of hospital information applications. The company never had the opportunity to either succeed or fail, since after about six months GE decided to terminate all of its computer activities including Medinet. Although Medinet was not given the opportunity to implement a working demonstration of the proposed language, known as Filecomp, the specifications for the language were most intriguing in that they included the initial structure for a hierarchical global file structure.

The main character of the next flashback chapter is one of the most imaginative and productive computer scientists it has been my privilege to know - Neil Pappalardo. I first knew Neil when he was a student of mine at MIT and did his senior thesis in my cardiovascular laboratory. He and Curt Marble, a fellow MIT student, joined me after graduation from MIT as Research Assistants studying cardiovascular system control. We were using mathematical models to analyze the feedback control of cardiovascular function and became heavily involved in the use of computers - first a PDP-4, then a PDP-7. In about 1965-1966, Neil and Curt tried to persuade me that we could develop a programming system that would support the development of medical information systems at MGH. For some months, I tried to discourage them from what I felt to be a radical and

obviously unproductive activity - after all, what competency and experience did a hospital-based group have in comparison with the giants in the field who were not yet able to provide a viable, reasonably inexpensive, easy to program, time-sharing system. Neil, however ignored my guidance, as was his usual habit, proceeded with the development of MUMPS, and in a few months, had a system that was exciting and promising. To this day, I have not been able to trace who first thought of that name, or why we did not come up with a more dignified title.

The development and use of MUMPS quickly became a dominant theme of our Laboratory. Indeed, it is my impression that one of the important reasons that MUMPS evolved into a powerful and easy to use language was that the development was carried out in an environment where there was very close communication between the potential users and the system designers. In our small group, there were no system analysts, no application programmers, no systems programmers - we were all problem solvers trying to develop a working system. In addition, we had the fortunate luxury of relatively stable support - NIH was at first not overly supportive of our work in creating the language, but because their investment in the MGH project was so large, and because they had no good alternatives for application development, they provided the funding to allow us to proceed.

The technical details of the first MUMPS implementation on a PDP-7 are of interest in comparison with the technology now available. The PDP-7 had 8K of memory (18 bit words) with three Teletypes and a 256 K fixed head disk. The complete MUMPS interpreter with input/output routines and buffers occupied 4K with active user programs residing the one of the 2K partitions. A major breakthrough occurred when we obtained our first PDP-9 computer which utilized a 24 K memory. The initial MUMPS systems were constructed before we had developed the global file handling system and DEC tapes were used extensively for data storage. One of our first ambulatory medical record systems had an active data base stored on over 100 different DEC tapes - not exactly a computer operator's dream. The development of the global system and the expanded core memory on the PDP-9 made it possible to undertake much more challenging applications. In the 24K version of the PDP-9, we were able to have 16 users running simultaneously - albeit slowly.

The years of 1967-1972 were exciting times in the Laboratory. We were able to implement operational information systems in a variety of areas and undertook initial developments in a host of challenging medical applications. The major organizing principle of our development was a "modular" approach. We argued that because of the difficulty in formulating a "total systems" plan, it was more productive to focus on identifying functional information processing units of medical activity and to provide well-defined and clearly bounded computer systems which could be explicitly integrated into the real and concrete medical needs of operating departments of the hospital. This modular approach made it easier to obtain agreement and cooperation at the departmental level, sharply limited the initial start-up costs, and simplified the cost/benefit analysis since the computer program was closely linked to one specific operations unit. An additional advantage which proved of great value was that this modular approach resulted in a "domino effect" where success in one department served as an attractive role model for development of modules for other departments. Lastly, a major advantage of the modular approach was that it facilitated flexibility and graceful evolution since we could make specific changes to one module without having a large, unforeseen or negative impact on other activities.

The first two major hospital systems which we implemented were the Chemistry Laboratory test reporting system and the Bacteriology test reporting system. The first part of the Chemistry Laboratory system was implemented in 1968 and has been operational since that time, 7 days/week, 24 hours/day with a down-time of less than 0.2% for the past 20 years. This system has been extended, patched, enhanced, modified, expanded, and marginally rewritten by dozens of programmers during the last two decades. This year, we are finally being forced to rewrite the system and discard the old programs. I doubt that there are many systems with this longevity; if there were a NIM archives for old code, I would nominate these Chemistry Laboratory Reporting programs.

Two of the early post-doctoral trainees at the Laboratory were Bob Greenes (now director of the Decisions Systems Laboratory of the Brigham and Women's Hospital) and Jerry Grossman (now President and Director of the New England Medical Center.) Bob Greenes played an active role in the early creation of MUMPS and, in addition, was the lead developer of a computer-based system using a dialogue between the physician and a computer-controlled display screen. His system for using this to collect progress notes in a hypertensive clinic was the subject of his Ph.D. thesis in Computer Science at Harvard - one of the first Ph.D.'s awarded in what we now call medical informatics. It is of historical interest that Ted Shortliffe worked in the Laboratory on this project while he was a undergraduate student at Harvard College. There were no commercially available light pens at that time, so we had to invent our own touch sensitive receptors - a series of metallic strips overlying the CRT screen. These metallic strips were part of a tuned circuit which had a frequency shift induced by a change in capacitance when touched. One annoying problem occurred in conditions of high humidity or when the users fingers were overly moist - in such circumstances the user would occasionally receive a mild shock. This Pavlovian reinforcement did tend to keep down the length of the notes that were generated with the system.

Jerry Grossman was one of the key figures in the Laboratory's first efforts in developing a computer-based ambulatory medical record. When the Harvard Community Health Plan was first planned by the Harvard Medical School Dean in the late 60's, we were asked to work together to develop a computer-based medical record system. When the plan opened its doors, our computer-based record system was in place - though not heavily loaded since there were only eight patients enrolled. It was in large part a tribute to Jerry's enormous energy and commitment that COSTAR survived through the growing pains of both HCHP and the changes in the information system. He guided COSTAR through a number of re-writes and extensions - for a time, he even acted as the Medical Record Room supervisor for HCHP. COSTAR was our first major effort to develop a system which could be made available to the community as a public domain supported product; probably the most amazing observation is that the system is still being actively used and supported and extended by over a hundred different sites. Since the code was written by over 40 different programmers over the past 20 years, you

can imagine that this system sets a new record for spaghetti code.

During the entire history of the Laboratory's existence I have enjoyed participating as a faculty member in the Department of Electrical Engineering and Computer Science at MIT. I have learned much from the students whom I have met in the different courses with which I have been associated. One of the most important opportunities I had was being one of the supervisors on the Ph.D. thesis of Tony Gorry (now Vice President for Institutional Development of Baylor College of Medicine.) Tony and I were fascinated by Homer Warner's early work on using Bayes rule in computer-aided medical diagnosis. We became interested in using mathematical models to assist in clinical decision making. Homer was very generous in sharing a large data

set of clinical findings in congenital heart disease. Tony demonstrated that a program could employ sequential decision-making to balance the risk of making a diagnosis against the cost of further testing and the value of the evidence which could be obtained. His work in 1967-68 was one of the first efforts to give explicit consideration to the potential value of information when deciding whether to collect further data. Tony's work was an important stimulus to my interest in sequential decision-making and to the potential role of computer programs in medical education. In fact, some of the most sophisticated computer-based medical education programs which we now write are still strongly influenced by my early collaboration with Tony.

The Laboratory is now almost twenty-five years old and much has changed since those early years. In the intervening years many wonderful individuals have worked on a variety of projects ranging from an automated medication system, to a number of laboratory and radiology information systems, to medical education programs, to different ambulatory medical record systems. I have been fortunate to be working in a hospital which has been very supportive and provided challenging opportunities and outstanding colleagues. I have also been fortunate in the support and encouragement that has been provided by the different funding agencies. Perhaps someday we will have a conference on what happened during the second and third decades of the development of medical information systems.

It is very tempting to become overly sentimental in recalling the history of the Laboratory. Flashbacks follow flashbacks follow flashbacks - memories become rose-colored with distance; I tend to remember the good and reinterpret the bad. However, preparing this paper does give me one opportunity which I greatly treasure, and that is to thank those of you who have been so important in providing stimulation, leadership, support, guidance, wisdom and, most of all, fellowship over the years. I have always deeply enjoyed the many different experiences we have had, the site visits to Peoria and Columbia, the study section and committee work, the reports we have worked on together. A number of you in the audience I count as personal friends, as individuals who have been vitally important in both my professional and personal life. For all that you have meant to me, I can only express my deepest appreciation, and for the years ahead, I look forward to more of the same. I hope that I can pass on to the younger generation some of the excitement and fun and fellowship we have shared together.

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THE LINC WAS EARLY AND SMALL

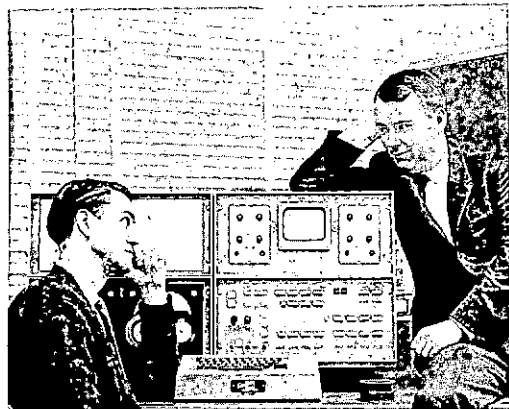
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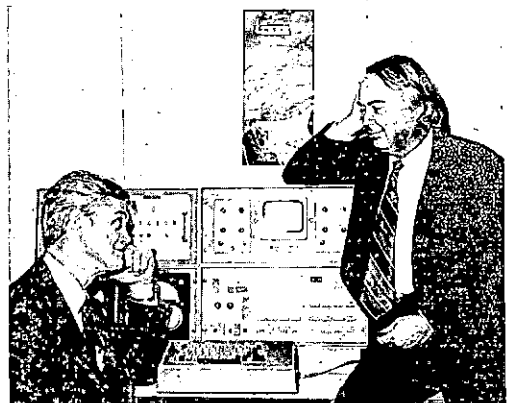
SUMMARY

The LINC represents one of the earliest attempts to put the stored program computer into the form of a general instrument for laboratory use. In a deliberate departure from the technology of Timesharing then just beginning nearly two decades of development, the LINC was designed for use by individual experimenters and thus anticipated features of the modern personal computer and personal workstation. Built at M.I.T. in 1962, its immediate forebears were the TX-0, ARC-1, and L-1 computers, in turn direct descendants of the M.I.T. Whirlwind and MTC computers. Of course the LINC in its day was neither personal computer nor personal workstation but simply the LINC.

The LINC was an outgrowth of interactions between two M.I.T. groups of scientists and engineers: the Communications Biophysics Laboratory interested in the quantification of neuro-electric activity, and the Lincoln Laboratory Digital Computer Group engaged in the development of advanced computers. Twelve LINC's were placed initially in biomedical research laboratories across the country under a unique NIH/NASA-sponsored evaluation program. Ultimately more than 1200 LINC or LINC variants were manufactured commercially for worldwide use. The basic system design went on to influence the design of the DEC PDP-4 and PDP-5 computers, which in turn helped to pave the way to the PDP-8.



1963: The author and Mr. Charles E. Molnar with a LINC. The photograph was taken in Cambridge following the first phase of LINC Evaluation Program activities in which groups of scientists were given special training at a one-month summer course at M.I.T.



1981: The author and Dr. Charles E. Molnar with a LINC in a recreation of the above scene following a Digital Museum Lecture (see wall poster). Eighteen years grayed us both. Several of the original LINC's, also grayed, were still in use in various parts of the world. (Photo courtesy of Digital Equipment Corporation)

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INTRODUCTION

Twenty-two-plus years ago — in September, 1963 — the last of about twelve freshly assembled LINC's was safely delivered by moving van from M.I.T. to its new home in California. By itself, perhaps, this would not have been considered particularly noteworthy. But the event marked the successful completion of Phase I of a remarkable and unprecedented program. The twelve or so LINC's assembled during the very hot Cambridge summer of '63 had been put together by their new owners themselves. Each of these pioneers would take full responsibility for trial operation of the instrument as a workstation in his own biomedical research laboratory, and was expected to use it in the mode we have come to call, in Alan Kay's powerful paradigm, personal computing.

The participants in this innovative NIH/NASA-supported program had been selected on the basis of how suitable such a laboratory instrument would be in their ongoing or planned research activities. Each participant had agreed to assume individual responsibility for using and maintaining the machine throughout a subsequent eighteen-month period that defined Phase II of the program. The LINC Evaluation Program, as it was called, had been announced in *Science* and in descriptive brochures sent to academic and research institutions around the country. Candidates had been invited to submit proposals responsive to the scientific and technical objectives of the program. Computer programming or hardware experience was not required; the necessary fundamentals were to be learned in a one-month intensive training and kit assembly program to be conducted at M.I.T. by the LINC design team. Ultimate disposition of the assembled instruments was to be determined upon completion of Phase II.

More than seventy proposals had been received and studied by a specially created LINC Evaluation Board composed of distinguished scientists and engineers from research institutions across the country. After careful review the Board had finally accepted just twelve. These represented the fields of psychology, physiology, genetics, pharmacology, biophysics, and neurology. The selected participants had been divided into two groups to be convened in July and August respectively, with each principal investigator to be accompanied by one associate or colleague.

By mid-spring of 1963, all of the personal commitments had been made and much of the LINC hardware was in manufacture. But apart from one operating system/assembly program that had been developed and tested by simulation on a larger machine, the Lincoln Laboratory TX-2, the only LINC software in existence consisted of a few programs that had been written for an earlier demonstration prototype. With only two months to go, the final design of the LINC itself had not yet been completed.

How had all this come about? What was the LINC and what were its design objectives? Why did the field of biomedical research play such an important role in its development? I will try to recount something of the early history in answer to

these questions. Like all such accounts of the introduction of a complex new instrument, the story is one of people, ideas, machines, and institutions and spans many years. As a principal instigator and designer of the LINC my perspective is limited to the events and circumstances that shaped only the earliest chapters. The full story must be left to others.

In what follows I will try to underscore and develop the title's assertion that the LINC, as personal workstations go, was early and small [1]. Early is evident; small, on the other hand, must be understood in the context of the memory capacity and the physical size of computers of the period. Since the machine's characteristics have been well documented (though not in the computer literature) I have indulged an urge to reminisce mostly about the people and events that really made the LINC experience such a rich and rewarding one. Some parts of the historical background may seem to be unnecessary embellishments, but I have included them in the hope that they will help in tracing the development of ideas and themes. The *dramatis personae* comprise extensive lists in both the computer and biomedical disciplines, and for the sake of simplicity I have kept professorial titles to a minimum and have arbitrarily 'Dr.'ed only those players who appear in character from the biomedical side of the stage. I hope that my friends will forgive me for this, as well as for any miscrediting of ideas and any errors or omissions of fact that may have settled into my own memory over the years.

BACKGROUND

Interacting with Whirlwind and MTC

Al Perlis and Doug Ross and I fondly remember the M.I.T. Digital Computer Laboratory Whirlwind computer, the machine on which I learned what little anyone knew about programming in 1952. One walked into it. What now sits comfortably on a small desktop, in those days required an entire room for the control console alone. Programming for its small electrostatic memory (1024 16-bit words on a good day) was a primitive affair carried out with the aid of heavily ruled coding forms on which to write out absolute-address instructions and octal numbers. [Confronted by the prospect of having to program in such a manner, Al immediately designed a new improved form that consisted of a large sheet of blank paper.] But its early users did indeed walk into the control room and for their assigned block of time, typically fifteen minutes or so depending on the time of day, the entire machine was theirs. In this regard the use of Whirlwind as a workstation of sorts was no different from that of many other early computers, especially in the universities. What makes the Whirlwind computer important in the history of the personal workstation is the fact that it was the first really high-speed machine with powerful interactive display capabilities [2].

But it was MTC that really drove the point home. MTC, the Memory Test Computer, was designed and built by Harlan Andersen and Ken Olsen to provide a working computer system in which to try out

the first ferrite core memory, a vacuum-tube driven 1K 16-bit unit engineered by Bill Papian then a graduate student under Jay Forrester [3]. Blocks of time measured in hours were available and the entire machine, quite similar in architecture to Whirlwind, now occupied only a single large room. Bristling with toggle-switches, pushbuttons, and indicator lights and provided with audio output as well as versatile CRT displays, it made interactive use a quite lively and memorable experience.

I suppose the idea of using even a very large computer such as the 1953 MTC just as one would use any laboratory tool was introduced to me by Belmont Farley, my teacher and collaborator in early computer simulation studies of neuron-like networks [4]. Belmont, a physicist by training and a man of considerable vision and strongly held convictions, joined the Digital Computer Laboratory shortly after my own move to M.I.T. to learn computerology. [I had almost become a physicist myself at one time, in what I now consider a close call; but that's another story.]

Belmont and I spent enormous numbers of hours interacting with MTC and with one another (he talked, I listened) as we tried out ideas, modified parameters, and studied displays of the simulated behavior of our strange little networks, grateful for such extensive access to such a powerful if not yet completely reliable machine. [A self-restarting test program was left running on MTC whenever the machine was otherwise unoccupied. In those pre-regulation days you could tune a radio to the frequencies being broadcast by MTC's long open-wire bus and hear the test program running, or trying to run, from several city blocks away. Sometimes when approaching by automobile for an extra-long simulation run in the dead of night the signal was clear enough for a decision to turn back home if things weren't going well.]

It was in these sessions that I began to learn from Belmont many of the basic attitudes toward computers that I hold firmly to this day: *Computers are tools; convenience of use is the most important single design factor — Big computers are for big jobs; small computers, for small jobs — Separate personal files are safer than files held in a common shared space — Digital computers should handle analog signals as well — and so on.*

In what would become a very important liaison, Belmont and I began to attend the seminars of the Communications Biophysics Laboratory, CBL, under Prof. Walter Rosenblith, later Provost of M.I.T. and presently Foreign Secretary of the National Academy of Sciences. Walter's group was concerned with the problem of quantifying neuroelectric phenomena. It was quite interdisciplinary in its approach and attracted students, post-doctoral fellows, and visiting scientists from many parts of the world. CBL had been developing various signal processing techniques. Much of CBL's work involved auto- and cross-correlation analyses based on data recorded on FM tape and then processed by analog devices. Work was just beginning on the analysis of the electrical signals from single neurons.

Our interaction with CBL started slowly. The Digital Computer Laboratory was absorbed into the recently established Lincoln Laboratory to become a

component of Lincoln's massive program in air defense. Our base of operations shifted fifteen miles west to Lexington and we were assigned to a new group charged with advanced computer development together with Ken Olsen, Bill Papian, Dick Best, Jim Forgie, John Francovich, Ben Gurley, and many other members of the former Digital Computer Laboratory staff. Belmont and I somehow managed to keep up our pilot studies in network simulation with much travel back and forth to CBL and to the MTC in Cambridge.

Bill Papian and others, bolstered by the immediate success of the 1K MTC memory (shortly thereafter replaced by a 4K unit) now began to build the largest core-memory array thought feasible, a 64K 36-bit unit. This array would be thirty-six times the storage capacity of the 4K MTC array and would certainly constitute a big step in computer memory technology. In my new capacity as leader of a small sub-group in logic design I made sure that its potential for further simulation and modeling work was kept in mind.

The Lincoln TX-0 Computer

It was a time of transistors. Ken Olsen, in charge of the sub-group in advanced engineering development, joined me in proposing the construction of a vacuum-tube machine of considerable size, the TX-1, as a suitable vehicle for testing the large memory array [5]. When this idea was turned down by Laboratory management (wisely enough) Ken and others began to develop transistor circuits in earnest. I began the logic design of a new machine, the TX-2, which would have about the same architecture as that of the rejected machine but would take advantage of the new circuits. It is interesting to note that one of the main architectural features of the TX-1/TX-2 design — multiple program counters used in what I badly termed multi-sequence programming [6,7] — was later employed to great advantage by Chuck Thacker in the design of the Alto workstation [8].

I proposed that we first build a much smaller, primitively simple computer that I had designed and named the TX-0 [3,9]. [We had already used up "1"; later Ken and I would say that we didn't build the TX-1 because we didn't like its color scheme.] The 18-bit TX-0 would use only half of the large memory array and would be quite simple in logical structure, maximally RISCy, one might say today. When the second half of the array was completed the full array would then be installed in the TX-2 on which design and construction would have been proceeding. The TX-0 would then be retrofitted with a new memory unit of some kind and serve as a front end processor to the TX-2, or perhaps simply be dismantled. In the meantime it would have served in early evaluation of the new memory and transistor circuits and would have been more than adequate to the task of network simulation as well as to other tasks more directly relevant to the Lincoln effort. Not a bad plan for an R&D program. It was adopted. The TX-0 was built and a three-year effort to design and build the TX-2 was begun [10]. In addition to powerful CRT display units designed by Ben Gurley, the consoles of both machines would ultimately bristle in the best M.I.T. tradition.

The simulation work Belmont and I were carrying out had long had the interest and support of Bill Papien. Appointed Leader of the Advanced Development Group, Bill actively encouraged further strengthening of the interaction with the CBL group. Students and scientists from Rosenblith's laboratory began to try their hand at digital processing of neuroelectric data on the TX-0 and later on the TX-2. One of these students was Charles Molnar, who was to become a primary catalytic agent in promoting sound relationships within and between the two groups. Charlie, I soon learned, was extraordinarily competent and talented both as an electrical engineer and as a student of biophysics. He shared the conviction that computer tools would play an important part in what was beginning to be called "the biomedical sciences" and proceeded to master the operational and technical details of both the TX-0 and the unfinished TX-2. Charlie and I began to develop a basis of collaboration that would lead to the LINC and to many other developments over the years.

As the second half of the large memory array neared completion it became time to decide what to do with the TX-0. Bill Papien suggested replacing its memory with the group's new transistor-driven 4K memory unit (about the same capacity as that of the earlier vacuum-tube-driven MTC unit) and then moving the entire machine to the M.I.T. campus. This would give a wider group of students and faculty an opportunity to experience the kind of hands-on interactive computer use that characterized our work at Lincoln Laboratory in the tradition we were carrying forward from Whirlwind and MTC.

By that time both of the Cambridge machines, Whirlwind and MTC, had been completely committed to the air defense effort and were no longer available for general use. The only surviving computing system paradigm seen by M.I.T. students and faculty was that of a very large International Business Machine in a tightly sealed Computation Center: the computer not as *tool*, but as *demigod*. Although we were not happy about giving up the TX-0, it was clear that making this small part of Lincoln's advanced technology available to a larger M.I.T. community would be an important corrective step. The machine was then being used in some very exciting work in interactive programming by Jack Gilmore (unfortunately never published) that anticipated much of what we do today, but Bill's argument that the group's attention would be shifting to the TX-2 prevailed. Arrangements were made to replace the memory, enrich the instruction repertoire, and move the modified TX-0 to the campus in Cambridge.

But where exactly should it go? The logical place, it seemed to me, was Walter Rosenblith's laboratory. After all, CBL was then using the TX-0 computer more actively than any other group of visitors from the campus and expanded use by George Gerstein, Charlie, and other members of CBL was expected. To my surprise Walter declined to accept the responsibility. I therewith gained an important insight about what would work in a small laboratory setting and what would not. It seems in retrospect that the TX-0, small as it was for its time and demonstrably useful in CBL research, was still too much "the computer" and not sufficiently

"an instrument". Its care and feeding and the constant need for justification might well have compromised CBL's research objectives. Walter's technical judgement, as usual, was correct.

The modified TX-0 eventually found a home under the larger umbrella of the Electrical Engineering Department, where it was used heavily by CBL and other groups and helped to train several generations of students in the interactive use of computers on-line. Somewhat later it was joined and largely upstaged by a PDP-1 computer (in some sense a production version of the modified TX-0) that had been donated to M.I.T. by the Digital Equipment Corporation and would later be used in some of the earliest experiments in Timesharing [3].

Timesharing had by then captured the imagination of much of the M.I.T. computer science community (not yet a science, of course; it would not be so until a few years later, when Al Newell, Al Perlis, and Herb Simon said, *Let there be Computer Science*, and there was). This seemed to me a bad idea and still does, the captive imagination aspect no less than the underlying premise itself. Improved access, yes; thrashing competition and waste, no. This is not to deny that Timesharing resulted in a huge and productive impetus to computer science at a critical time. Certainly it has given much gainful employment to computer scientists and manufacturers and salesmen over the past twenty years or so. But it seems to me that we could have done better than to divert so much of our attention and resources to trying to make good the promise of a patently unattainable "sensible simultaneity" for all. [I may not always be right, but at least I am consistent. When working out the multi-sequence programming idea some years earlier I had considered and rejected the notion of competitive time-sharing by independent human users as grossly inefficient; much later at the dawn of the Timesharing Era I had no qualms about turning down a suggestion of Ed Fredkin's to set up such a system for the multi-sequence TX-2 (much to his disappointment and, as I recall, disgust); in meetings of the M.I.T. Long Range Study Committee in 1961 I objected (to no effect) that campus-wide Timesharing so enthusiastically being rationalized as a panacea would not be able to deal with real-time work such as CBL's and moreover would inhibit the development of any interactive computing that involved complex displays. The M.I.T. Study Committee Chairman and I both declined to sign an otherwise unanimous final report. He thought it didn't promise nearly enough. Walter urged me to write a minority report, but I knew a steam roller when I saw one and went on to other matters.]

The ARC and the L-1

Not long after the decision to move TX-0 was made, Charlie and I met with Moise Goldstein and Robert Brown of CBL. The subject of discussion was the possibility of building a digital device to extract stimulus-evoked neuroelectric potentials from a background of unrelated electrical activity by means of a summation technique then being tried at CBL on analog equipment. Aha! A digital instrument for Walter! I immediately agreed to take on the design task.

The logic design of the instrument fell into place readily enough. I simply used many of the transistor logic plug-in modules already designed by Ken Olsen and Dick Best for the TX-2, and my colleague Henry Ziemann neatly solved the problem of memory by working out the details of a very small 256-word core array. An 18-bit structure seemed about right for the job and nicely matched that of the TX-0 with which the instrument might later be in communication. I designed two simple operating modes to provide response averaging and amplitude histogram compilation, both modes to be wired into the control circuits. With electronics, control switches, lights, CRT, plotter, and paper-tape punch, the whole thing—even without an analog-to-digital converter—required a cabinet about the size of two refrigerators turned on their sides. Today we would think it a machine of rare ugliness (as an unkind journalist once said of my automobile). We named it the ARC, an acronym for Average Response Computer [11].

The ARC was completed in early 1958. Though not all that much smaller than the TX-0, at least it was portable and rolled through doorways. I rode it in triumph into the Communications Biophysics Laboratory and it was almost immediately put into service. After about a year of operating experience the CBL staff decided that a third mode for compilation of time histograms of single neuron activity would be useful, and this was duly wired into the ARC control. Over the next several years the ARC served in a wide variety of studies, teaching researchers many new aspects of the neuroelectric behavior of the brain. It also confirmed my belief that there were indeed useful things that small digital computers could do in the laboratory.

But wouldn't it have been better to program these operating modes rather than wire them into the control circuits? I had since taken just that approach in designing an extremely simple stored-program computer of very limited capability, the 256 10-bit word L-1, for use in a special project [12]. There was no doubt in my mind that the far greater flexibility of the stored-program approach was of enormous value even in computers small enough to be considered "instruments" for laboratory use.

At the first symposium of the Brain Research Institute held at UCLA in 1960, Belmont and I joined with Walter and several members of CBL and Dr. M. A. B. Brazier (of both CBL and the BRI) in discussing some of the viewpoints and accomplishments of the M.I.T. work [13]. In my presentation I contrasted the stored-program and wired-logic approaches:

The TX-0 is a relatively small but powerful stored-program computer. A rough comparison of the ARC and the TX-0 computers is illuminating. Both machines operate on 18-bit binary numbers, control analog-to-digital converters, have cathode ray tube displays, can be controlled by the experimenter, and hold about the same number of circuits derived from the same body of electronic technology. The TX-0, however, has about 8000

registers of digital storage and is organized as a general-purpose device.

It is quite simple to program the TX-0 to act very much like the ARC; in fact this has been done, requiring an investment of effort measured only in hours. The TX-0 can in addition generate quite varied displays of the data and of results of analysis, and can be programmed to carry out exceedingly lengthy and complex operations if desired. This flexibility of behavior is characteristic of the stored-program computer and is obviously of great value.

It is extremely important, of course, to provide for procedural flexibility and easy access to machines of this type in order to realize their full potential. Ideally the researcher would have the general-purpose computer in his laboratory for use "on-line", enabling him to observe and act on the basis of the calculated results while the experiment is in progress.

Stored-program computers like the TX-0 are beginning to appear in commercial form and there is reason to hope that these machines, or perhaps other general-purpose machines with a capability somewhere between that of the ARC and the TX-0, will find their way into the laboratory.

Well, there it was. Clearly, the thing to do was to go off and design a machine that would fill the niche I had just defined.

DESIGNING THE LINC

It has been both pleasurable and dismaying to look over my design notebooks after a lapse of nearly twenty-five years. I can easily relive the the exhilaration and sense of discovery in the pages detailing those rare ideas that "worked" and survived and were good. But there are other pages, too, some of them recording in distressing detail my false starts, muddled thinking, and irredeemably bad ideas. The design process is like that, of course; yet one always hopes that the overall record will reveal a higher order of thought and development. It is embarrassing to report, therefore, that the LINC design notebooks do not, on balance, document the workings of an orderly mind.

Following the October symposium at UCLA I increasingly began to sketch and doodle on various handy surfaces. It seemed to me that I now had most of the keys to the design process: a firm belief in the soundness of the goals and a good sense of the functional requirements, the general technology to be used, and the bounds of acceptable size, complexity, and cost. What I was trying to find was some gimmick, some architectural idea to start the process off in any promising direction. Taking the principal constraint to be the factor of acceptable cost I arbitrarily set a target of

\$25,000. This figure, relatively small for computers as we then knew them, seemed about right. It was about the size of one staff salary, for example, or about what a department head could authorize for equipment without the approval of higher management, and so on. Remarkably enough it was little more than twice the cost of the a-to-d converter used with the ARC. Was there some architectural scheme that might yield a useful laboratory-size computer subject to this cost constraint, something that would propel me out of the back-of-an-envelope phase and into the discipline of the engineering notebook?

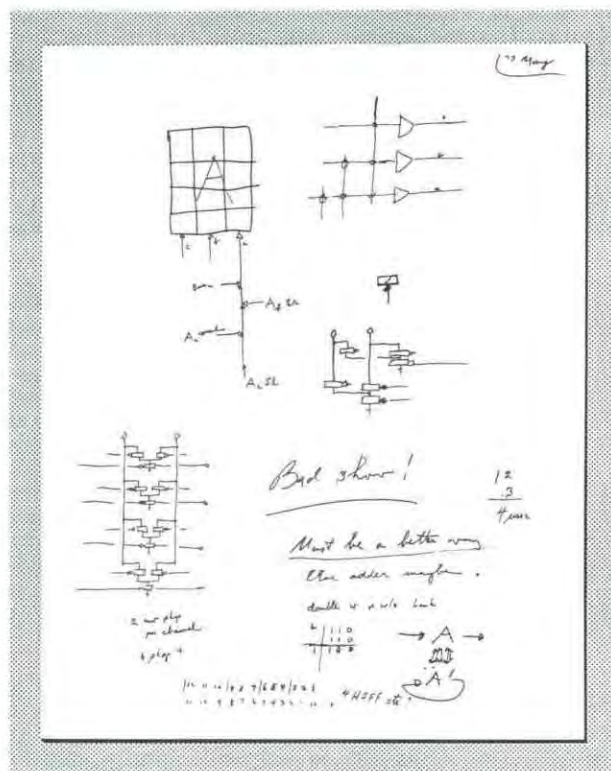
First Attempts

Volume I of my three LINC notebooks carries the dates May 24 to July 4, 1961 — roughly Mother's Day to the Fourth of July. I had found a starting gimmick in the form of a serial-parallel scheme that appeared to reduce cost without seriously compromising speed. I would take advantage of a new family of plug-in circuit modules then being produced by the Digital Equipment Corporation. Ken Olsen and Harlan Andersen had left Lincoln Laboratory to found DEC in 1957 and were followed shortly thereafter by Dick Best, Ben Gurley (who later engineered the PDP-1), and others from the Lincoln group [3]. The circuit modules DEC was now manufacturing, forerunners of the integrated circuit chips that were not to appear for several more years, seemed quite suitable.

I knew that the machine would need two small tape units about the size of the "snapshot" unit I had proposed earlier for use with the TX-2 as a personal file input-output device and that my colleague Tom Stockebrand had tried to make. These units would have pocketably small reels for programs and data and would use block addressable magnetic tape like that of the TX-2's huge and frightening device for on-line files [14]. [The TX-2 tape unit used 14 inch reels of 3/4 inch tape, a very large inertial load. Its design was based on an observation of mine that the TX-2's multi-sequence capability made it possible to eliminate the usual requirement for finely controlled tape speeds, and I further proposed that the positions of all bit-cells on the tape be fixed by prerecording timing and blockmark tracks. In programming use, the resulting unit's tape speed varied markedly with wrap diameters, as did inertias and vibrational resonances. At top speed in block searching mode the tape's linear velocity reached 60 miles per hour! The whole room shook.]

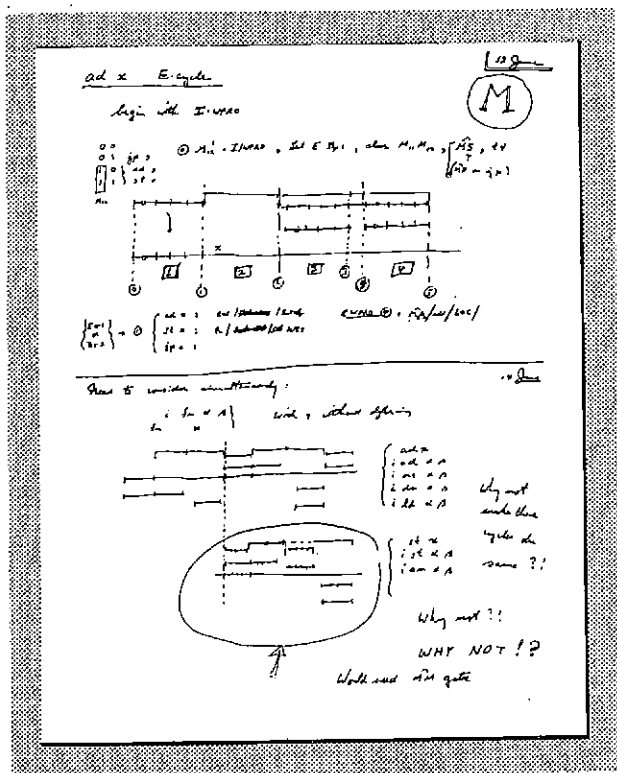
Most of the work over these first two months went into thinking through the details of the serial-parallel architecture and an appropriate set of machine instructions. I knew that I had to build in a-to-d conversion channels and devote some of them to console potentiometers for convenient knob control of continuous variables (a good idea contributed by Belmont). I knew that CRT display would have to be inexpensive and would therefore use the same point-display technology that appeared in all of the M.I.T. machines. A more difficult task, however, would be thinking through the control for the tape units and developing the right set of block transfer modes for their use. The 1K or 2K 12-bit words of memory that seemed feasible

under the cost constraint would not permit lengthy program routines for tape operation. These routines would therefore have to be wired into the central control circuits (of course there were no ROM chips in those early days). Block addressability of the tapes would help in running useful programs in the very small memory, the sort of thing we now do with disk systems.



The 27 May (1961) page from the LINC design notebooks. Early design was based on a serial-parallel logic using 4-bit shift register circuit modules made by DEC. Design progress was variably good.

I worked at home. Early in the design work I returned to the Laboratory briefly for an informal exposure of ideas to Charlie and Belmont and other members of the group, among whom were Severo Ornstein and a newcomer, Mary Allen Wilkes. There was a lively interest in what I presented as a "Linc". [I had thought that a generic name for this kind of computer would be useful and had decided on one that suggested the instrument's Lincoln Laboratory origins; Linc would be promoted to LINC by later events.] Following the meeting Severo and Mary Allen began to try programming with the proposed instruction set and I returned to the task of filling in design details. Charlie began to communicate his enthusiasm for the Linc scheme to CBL. Walter himself was later reported to be envisioning a relationship between a scientist and a computer similar to that between a scientist and a microscope. All was going well.



The 13 June (1961) page from the LINC design notebooks. Timing diagrams still appeared to support the serial-parallel scheme and new ideas were still emerging.

Alas, the serial-parallel approach turned out to be a false start. One month after its first exposure I had put enough of the design in place to establish the cost of the modules required by the central logic alone. Even without input-output devices or the core memory I had already used up my \$25,000. Gad. The final entry in volume I is the single line: "Crisis in River City!"

The Prototype Linc

For the next several months I concentrated on simplifying the design and detailing the tape unit and its control, the most complex part of the machine and the largest single unknown. Much of my earlier work translated readily enough into a more straightforward 12-bit parallel form. Somewhat to my surprise this yielded a substantially lower cost. So much for gimmicks. Notebooks II and III record a great deal of work over the remainder of the year in refining the instruction set and developing simple operating modes for the tape units. Sketches for the tape transport mechanism and console appear here and there.

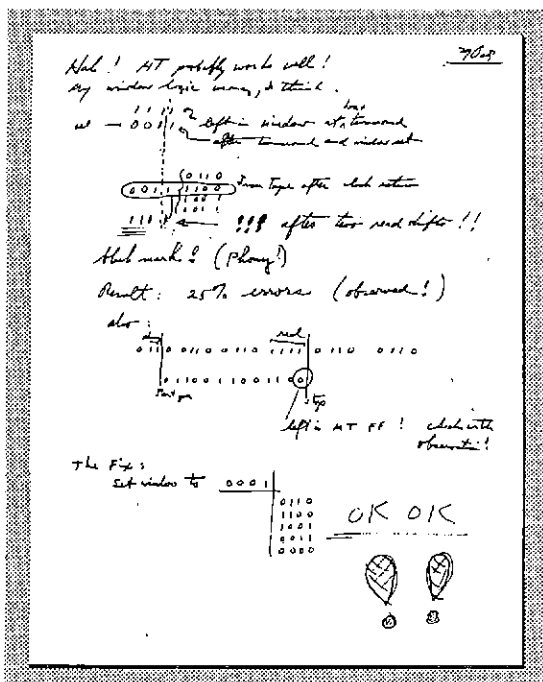
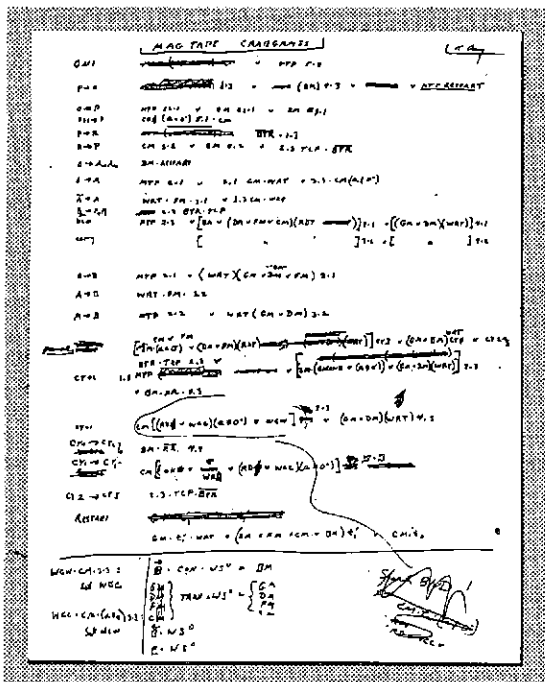
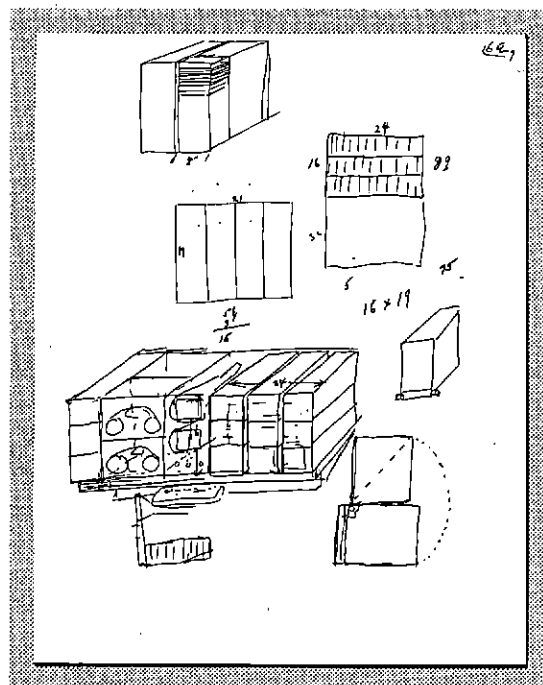
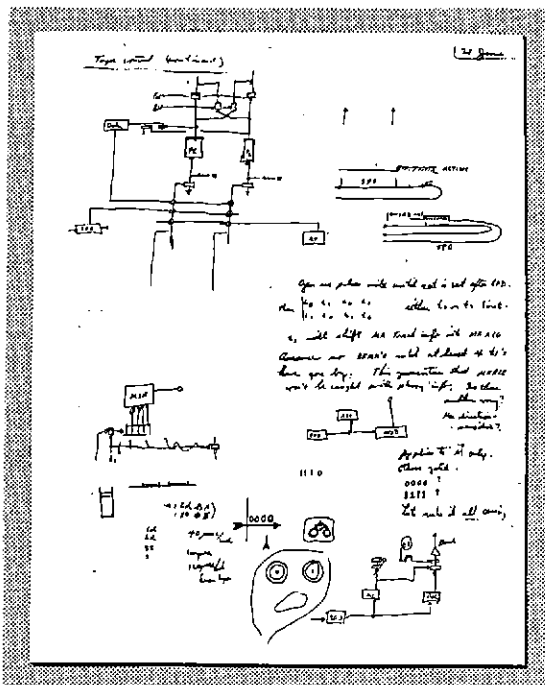
The need to build up a project effort at Lincoln began to demand more and more of my time as other members of the group joined in. Tom Stockebrand and I built a working model of the new tape

unit, with Charlie contributing helpful insights from his experience with its fearsome progenitor, the giant tape unit of the TX-2. Severo designed and built a special subsystem to pre-mark tapes with the required fixed backbone of block addresses, timing signals, and control code patterns. Hershel Loomis and I assembled a tape unit exerciser/tester using DEC building block logic modules and established that the Linc tape equipment would indeed function as I had hoped. We were on the right track.

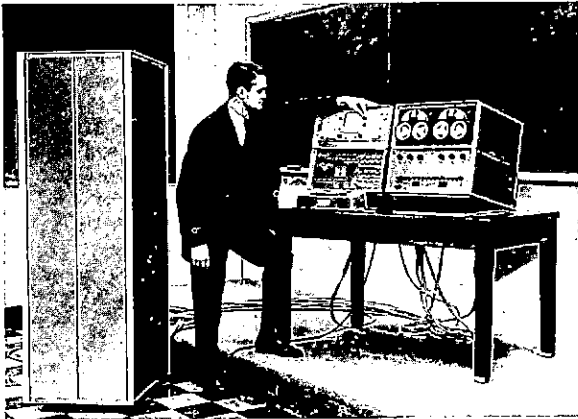
By early September the instruction timing diagrams had been completed in enough detail to enable Mary Allen to write a Linc system simulation program for the TX-2 and begin to develop a compact machine-code assembler for the proposed machine. Bill Simon, another newcomer and a remarkably creative scientist and engineer, designed a dual-scope alternative to the single-scope unit we eventually settled on, and began to write a number of test and demonstration programs. Norm Kinch, my right arm in matters of making things happen, began to produce large working drawings of system logic based on my notebook sketches and placed orders for parts as they emerged from the design. Severo and others helped with details of package layout and wiring lists. Charlie reviewed the design of the proposed 1K 12-bit memory system and watched over general engineering specifications. The final entry in Volume III was dated Christmas, 1961. Construction of the prototype Linc was already underway.

We hoped to complete the Linc prototype in time to take it to Washington for a demonstration in April at the forthcoming National Academy of Sciences Conference on Engineering and the Life Sciences. This had been urged by Walter and by Bill Papian as an excellent way to introduce the machine to a broad scientific and technical audience. Under this time schedule pressure but with tireless support from an enthusiastic technical staff, the Linc began to take shape. Hand-wiring of the electronics cabinet took its toll in anxiety and time over the ensuing weeks, as did the slow accumulation of special equipment and parts. But Norm kept the construction pretty much on schedule and the machine was completed in late February. It was working well enough for a Laboratory-wide demonstration at the end of March, 1962. The entire Linc group was justifiably proud of its accomplishment.

The demonstration prototype consisted of a set of four box-enclosed console modules, each connected by 20-ft long cables to a common electronics cabinet now the size of only one refrigerator; this general configuration would be used in all subsequent "academic" versions. One module, its box mostly empty, held a control panel that provided switches and register indicator lights (remember those?) together with speed and audio control knobs and so forth. A second module held a 5" CRT display adapted from a laboratory oscilloscope. A third module held the dual tape transport mechanics, while the fourth held a set of potentiometer knobs and jacks for analog input together with connectors for future input-output equipment. As an option for crowded laboratories, all modules could be removed from their boxes and mounted in standard equipment racks if desired. [Somewhat embarrassed



by the size of the electronics cabinet, we adopted the point of view that it was only the console modules, taken together, that constituted the instrument itself; the rest was merely the electronics that made it all go and would be tucked out of sight in any convenient closet. We expected the cabinet eventually to disappear with advances in electronic packaging. It did, of course; but then so, eventually, did consoles.]



The Linc system demonstrated at the Lincoln Laboratory auditorium in March, 1962. Four console modules are connected by 20-foot cables to a cabinet holding the required digital electronics. The demonstration consisted of running a few simple programs toggled in by hand in advance.

The National Academy of Sciences Demonstration

Charlie, Norm, Bill Simon, and I took the Linc to Washington as planned and the National Academy demonstration was well if somewhat uncomprehendingly received [15]. Bill had arranged for closed circuit TV equipment and had set up several monitors about the meeting room. Charlie and I had spent the night before—all night—trying to fix some unexpected problem in the arithmetic element, crawling around the floor of our suite at the conference hotel with test equipment and soldering irons and discovering only by the dawn's early light that just outside our room there was a huge broadcast antenna tower that had been flooding everything with electromagnetic noise.

Norm commandeered one or two people from the hotel staff and moved the Linc to the meeting room for the presentation while Charlie and I dressed, Charlie in his Air Force uniform since at that time he was completing his military service at the Air Force Cambridge Research Laboratories and had to appear in official garb. I stepped to the podium not knowing whether the machine was going to work or not, Charlie still frantically toggling in program parameters and trying out the demos. But at the last possible moment he slipped me a scrap of paper that said, "The following programs have my confidence: ...". The Linc performed perfectly. Whew! The only question asked, Charlie recalls,

came from an older gentleman who seemed to be quite interested in the durability of the wiring insulation. He was from the Smithsonian.

NIH Interest

After the Academy meeting Norm moved the Linc to one of the laboratories of Dr. Robert Livingston, Scientific Director of both the Institute of Neurological Diseases and Blindness and the Institute of Mental Health. There Charlie connected the analog-to-digital input channels to a multiple electrode array implanted in the brain of one of the lab's mascots, a cat whose name, I believe, was Jasper. In short order he wrote a small program that displayed on the CRT the average neuroelectric responses of the behaving animal. The Linc was successfully performing its first scientific task.

The writer Sam Rosenfeld, in a background paper prepared for a seminar held at NIH in celebration of the twentieth anniversary of the LINC, quotes Dr. Livingston's recollection of the event [16]:

It was such a triumph that we danced a jig right there around the equipment. No human being had ever been able to see what we had just witnessed. It was as if we had an opportunity to ski down a virgin snow field of a previously undiscovered mountain.

[Jasper merely purred and looked pleased.]



Jasper, one of several animals used in experimental work at a National Institutes of Health laboratory. The other end of the cable leading from the cat's head was connected to the Linc in a 1962 trial, the Linc's first scientific assignment.

It must be reported, however, that we did not have much success the next day when the Linc was moved to the laboratory of Dr. Mones Berman to see what it could do to isolate a very fast fluorescence transient produced in a particular biochemical reaction. Severo and Mary Allen answered an emergency call and came to Washington to help, but to no avail. Bill Simon would later write a superb program for the general problem of exponential decomposition but the limits of Linc speed had been reached.

Nonetheless, the interest of NIH had clearly been engaged. The National Academy of Sciences had already made the suggestion to Dr. James Shannon, Director of NIH, that he set up a committee to monitor and encourage the development of computer technology relevant to biomedical research. In response, Dr. Shannon had established the Advisory Committee on Computers in Research. This committee, among whose members were both Dr. Brazier and Bill Papian, had been following the M.I.T. activities closely. The Linc demonstrations at NIH had in fact been arranged by the committee's executive secretary, Dr. Bruce Waxman, who would shortly take further initiatives leading to the funding of a Linc evaluation program.

Linc Becomes LINC

The group at Lincoln had been joined by Dr. Thomas Sandel, a neurophysiological psychologist who had been conducting auditory research at CBL. Tom had organized and hosted an NSF-sponsored workshop the previous summer in which some of the M.I.T. computing techniques were shown to an invited group of biomedical researchers. He now proposed to use the Linc in a repeat of the workshop to be held in the summer of 1962. Plans were approved and a well-attended workshop was held during which several new Linc programs were written and new applications were investigated. [An amusing side benefit: In programming one of the data recording tasks we discovered that we had neglected to wire in a pathway for the signal specifying the initial direction of tape motion. Since the tape units were designed to search for designated blocks in either direction (now at a sedate though still uncontrolled speed of about 3 miles per hour), the occasional misbehavior had been self-correcting and had largely gone unnoticed.]

We began to think in terms of expanding the work. Bill Papian had been given to believe that under the right circumstances funds for support of a larger program in biomedical computing would be forthcoming from NIH. Charlie and Bill Simon and I were already beginning to modify and improve the design of the Linc so that a number of soundly engineered replicas could be made, and Tom Sandel was proposing to set up a small lab in space adjacent to the TX-2 for relevant biologically oriented work. But it was not to be. Lincoln Laboratory management, sensing that there would be serious organizational difficulties in administering such a program within its established framework, firmly rejected both the expansion and "wet" lab proposals. Instead, we were invited to find a more suitable home for any further work. In reporting to a stunned Linc design team the management's decision and my own decision to leave, I announced

that "Linc" had just become "LINC", an acronym for Laboratory INstrument Computer.

The principals subsequently spent several disheartening months trying without success to find a "suitable home" for the continuation and extension of the work to which they were now deeply committed.

THE LINC EVALUATION PROGRAM

Toward the end of 1962, Walter Rosenblith put forth an imaginative proposal: M.I.T. would act as host institution in a multi-institutional, multi-disciplinary endeavor to be called The Center for Computer Technology and Research in the Biomedical Sciences; faculty and staff from several New England universities would join in providing the scientific and technical substance of a long-range program; a Center Development Office would immediately be set up to work out details, secure multi-institutional blessing, and formalize a proposal to NIH; and finally, to avoid loss of momentum the LINC team would immediately be taken in under the CDO wing to complete the redesign effort and mount a program for the dissemination of LINC technology.

This proposal was widely accepted almost at once. Funds for the establishment of the CDO, with Walter as Director and Bill Papian as Associate Director, magically appeared. Arrangements were made with Lincoln for the transfer of staff and equipment, and the entire biomedical research computer effort at Lincoln Laboratory, together with several members of CBL, moved to new quarters next to the campus in Cambridge in January, 1963.

Redesign of the LINC

The next several months were ones of intense activity as we worked hard to complete the redesign in time for what was now formally known as the LINC Evaluation Program. Construction of 16 LINC's was authorized under the formal program. Twelve of these machines were to be assigned to biomedical research scientists selected by a nationally constituted LINC Evaluation Board for trial use in their own laboratories following a special Phase I training program at M.I.T. Four machines were to remain with the design team for coordination of Phase II evaluation activities and further refinement of the instrument itself. Given the new CDO framework Dr. Waxman of the NIH Committee, in a dazzling display of civil service at its best, had been able to earmark about half of the needed funds from NIH and had persuaded Dr. Orr Reynolds of NASA to put up the remainder from NASA's recently established Bioscience Program. In parallel with this activity NIH assembled the necessary committees to review the much larger proposal for the Center itself, and with amazing smoothness and speed authorized a huge M.I.T. research grant of an unprecedented scale sufficient to warrant announcement on the front page of the New York Times.

The idea of providing replicas of the LINC to individual researchers seemed quite natural. Tom Sandel had outlined just such a plan following the summer workshop the previous year and the idea had taken hold immediately. Charlie had then suggested, only partly in jest, that the computers be

put together by the workshop participants themselves and I had promptly taken the idea quite seriously as an excellent way to teach the inner workings of the LINC. After all, it would be up to the participants to keep their machines running, wouldn't it? What better way to ease these good people into the discipline of digital systems? We would gather the parts and subassemblies together in the form of a kit and provide assembly instructions and any necessary documentation. This would not only keep the costs down but would also encourage later participation by other interested individuals.

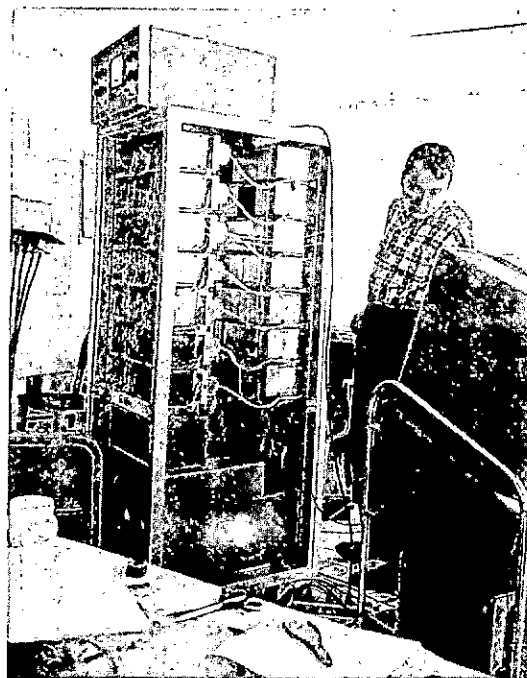


William Simon with an interim version of the LINC. The dual-display module provided both long- and short-persistence phosphor CRTs. Six potentiometer knobs supplied input parameters.



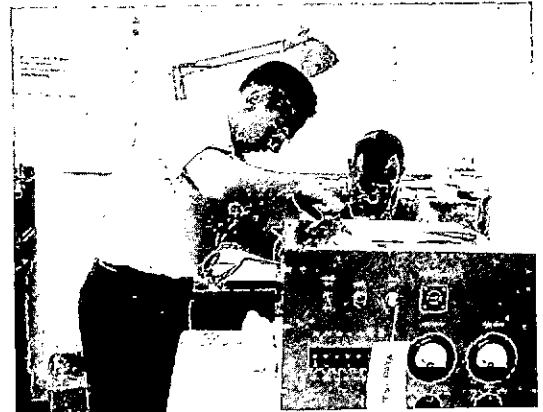
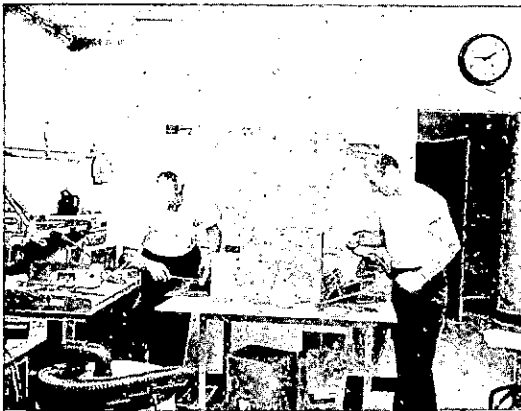
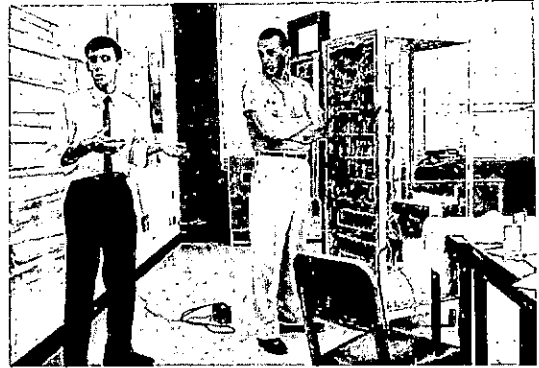
Technicians assembling wired frames for the LINC electronics cabinet. About twenty of these cabinets were required for the summer program.

Again the projected time schedule was extremely tight, especially for a development group in an academic setting. But morale was very high as it always is under such circumstances and every member of the now somewhat expanded design team proceeded to put in a magnificent performance. Charlie designed new circuits for the memory (now modularized in two 1K units with only one to be included initially) and completely reworked the magnetic tape unit read/write amplifiers and motor control circuits. Bill Simon redesigned the a-to-d circuitry and worked out a new single-scope system for the display module. Severo expertly refined the tape control logic and incorporated the tape pre-marking subsystem. Mary Allen traveled back and forth to the TX-2 at Lincoln Laboratory to update the LINC simulator and complete the new LINC Assembly Program, LAP3. Don Malpass joined us temporarily from Lincoln and did an outstanding job of designing the power supply and the interconnection system, the high-speed computer's Achilles' heel if not very skillfully handled. Norm Kinch prepared and endlessly updated the necessary drawings, and supervised our support staff as well as the beginning-manufacture of subassemblies by local vendors. I concentrated on the surprisingly difficult job of working out the details of console control and the proper arrangement of indicators and switches, and generally tried to keep the overall program on target.



Charlie debugging a prototype of the final LINC system. Modifications to the frame wiring were few but had to be made to all frames being assembled by a local vendor.

One month to go. Parts and subassemblies were continuing to arrive and the final LINC prototype neared completion. Mary Allen finished off the layout of the central control logic. Mishell Stucki, a man without peer in attention to detail, organized the wiring lists in a form suitable for the electronics frame checkout so critical to the success of the kit concept. Mort Ruderman of DEC took personal responsibility for assuring that sets of DEC modules, about 90% of the required electronics, would arrive on time. Howard Lewis and Dan Calileo and others stepped up the pace of special parts assembly under Norm and Charlie's supervision. Don O'Brien saw to it that the extensive and growing documentation was kept in good shape and had the assistance of Henry Littleboy of Massachusetts General Hospital. Severo was everywhere. One could not have hoped for a more dedicated and competent team.



(Top to bottom) Severo Ornstein (left) and Prof. Jerome R. Cox of Washington University review last-minute problem; Bob Brown (left) and Tom Sandel examine incoming power-supply; I check the wiring of a control panel module.

(Upper) Norm Kinch (left) and Dan Calileo repairing prototype power supply; (lower) Howard Lewis and Dan making "final" wiring changes to the electronics frames. Several additional modifications were later found to be necessary and were added, using white wires to avoid confusion with color-coded frame wiring already documented.

[Phase I photographs taken by Bill Simon.]

One week to go. One or two frames had been completely wired but there was still difficulty in obtaining the necessary test equipment to verify wiring accuracy. A last minute circuit problem that Charlie had discovered was overwhelmed with the help of Maynard Engbretson and Prof. Jerome R. Cox (a member of the Evaluation Board), who made

a special trip from Washington University in St. Louis. Tom Sandel, Chairman of the LINC Evaluation Board, monitored progress with increasing anxiety. Charlie and I maintained a facade of manifest confidence that masked serious concern.

Phase I: The LINC Summer of '63

On July 1 the first group of visitors arrived, some of them with golf clubs they would never use. We immediately put them into a crash course on the theory and use of computers, a holding action managed by Mary Allen and Irving Thomae and Severo for the two more weeks it would be until the kits were ready.



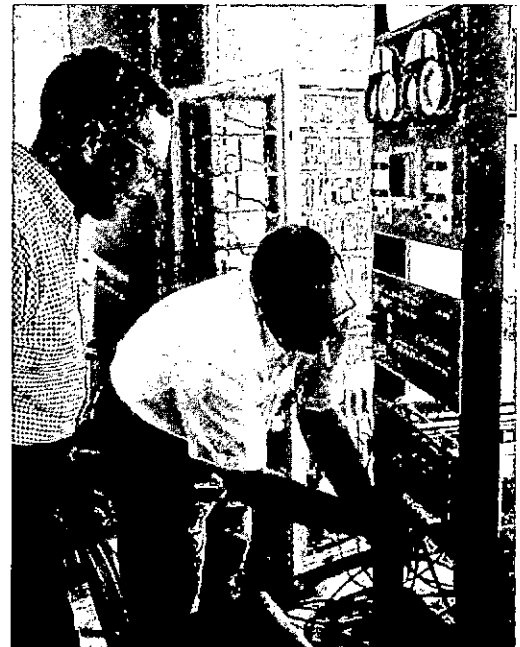
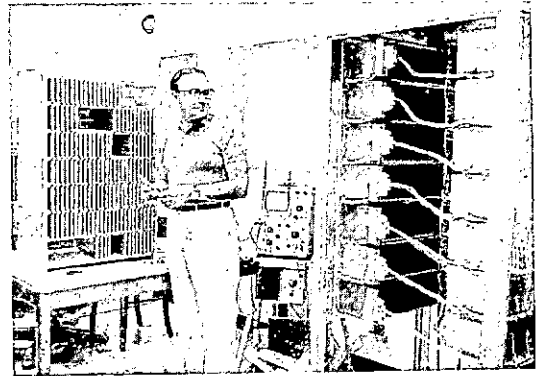
(Top to bottom) Severo explains LINC logic to the first group of visiting scientists; Irving Thomae reviews timing diagrams; Mary Allen Wilkes shows LINC programming.



(Upper) Tom Sandel (right) in discussion with Dr. Gerhardt Werner of Johns Hopkins University; (lower) Mary Allen works on a program using rack-mounted equipment.

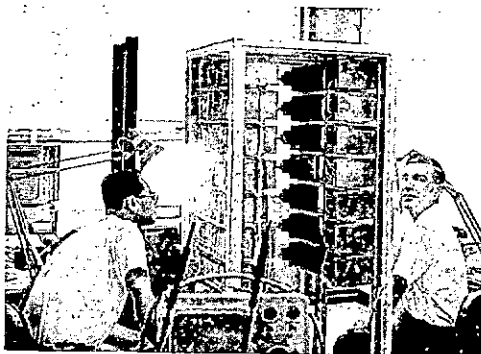
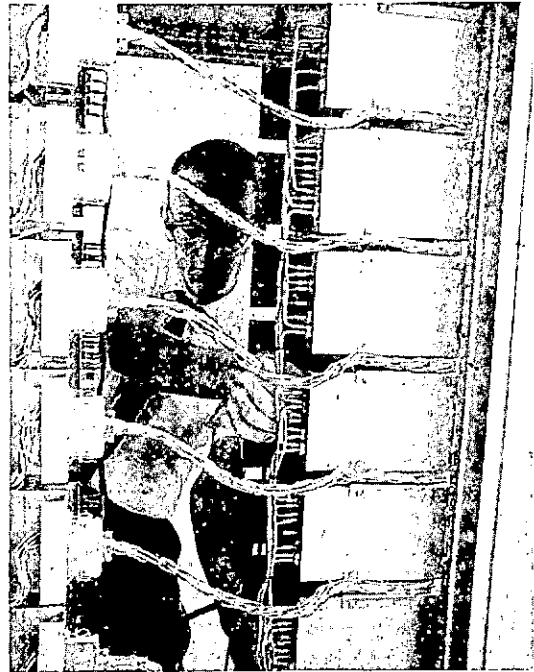
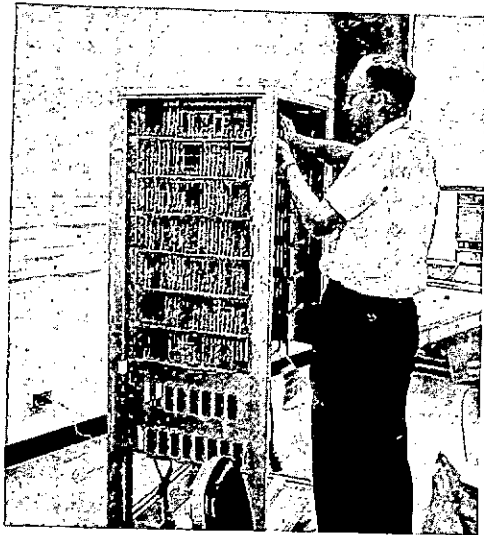
While classes were proceeding, the rest of us worked over the electronics frames and completed the job of checking the wiring, using Mishell's well-organized lists. The only part of this miserable and boring task we found rewarding was a sparkling Christmas-tree light effect produced by the test equipment. We found only a few wiring errors and fixed them.

Finally the assembly process began. To our delight and relief all went smoothly, though many long days and nights of exhausting work were still required to make up the lost time and correct minor design mistakes as we found them. The visiting scientists energetically and with much spirit and enormous dedication to the task proceeded quite successfully to bring all six or so LINC's to life.



(Upper) Dr. A. J. Hance examines his tape unit module. Tape unit modules were almost entirely electromechanical; one critical component was a rubber-band. (Lower) A group of visiting scientists mount display units in staging racks.

(Top to bottom) Dr. G. F. Poggio contemplates the plug-in unit installation task; Drs. N. Bell (left) and R. Stacy with staging rack; Dr. J. C. Lilly installs a modification while Mishell Stucki (rear right) ponders a problem.



(Top to Bottom) Dr. J. W. Woodbury installs a plug-in unit; Charlie discusses a point with Dr. K. Killam (right) while Dr. Hance nods (it is 2 a.m.); Drs. C. D. Geisler (left) and J. E. Hind examine wiring.

(Upper) Dr. C. A. Boneau reaches into his cabinet to make an adjustment. (Lower) Drs. F. S. Grodins (left) and J. E. Randall wrap interconnection cables.

Each of the visiting teams was required to write and demonstrate a small program representative of the work of its home laboratory. With the completion of these final assignments, the machines were packed up for shipment and the entire group of hosts and visitors, now fast friends, celebrated with great exuberance at a farewell banquet.

The M.I.T. hosts had only three days to recover before the second group of visitors arrived. This final session of Phase I went more smoothly than the first, with less pressured teaching and more time for thoughtful assembly. Once

again the visitors carried out all of their assignments with flair and great good humor, and again—on time—the LINC's were packed up for shipment. Our final banquet this time was an occasion for sober reflection on the magnitude and importance of what we had all achieved.



Moving day. Although some parts were crated for transportation, the electronics cabinets were simply taped up and carried in moving vans as furniture. Most of the machines were moved in this manner and all arrived safely at their new homes in laboratories across the country.

The LINC was now well and safely launched and in good hands. Charlie and I had little doubt of its ultimate success.

For the most part the participants had all taken to the unfamiliar fairly well. For those few who had already worked with computers, the general acceptance of machine-level programming as the price of dealing with such a small memory had been cheerful enough. Productive software, however, would not begin to accumulate in the various laboratories until the following year; the first published version of the programming manual, the year after that; and the first edition of the final assembly program, LAP6, not until 1967.

We had had to formulate both teaching and assembly procedures as we went along, but this resulted in only a few bruised knuckles and egos and a few inefficient hours (one of the visitors, a neurosurgeon, did have difficulty adjusting a tiny slotted-screwhead potentiometer deep within the recesses of the electronics frame, as I recall). Fixing design mistakes and modifying the circuits and wiring to reduce system noise meant repairing all machines in parallel. Each machine, by the way, had required a budget outlay of about \$32,000, or so the accountants told us. Not too bad a miss.

Throughout it all we had been sustained in our endeavors not only by our boundless energy and enthusiasm, our spirited sense of adventure, and our deep reserves of unshakeable conviction and commitment, but also by the Fox & Tishman Restaurant of Kendall Square, Cambridge. The F&T's sympathetic management and colorful staff fed and otherwise refreshed us at all hours of the day and night. [Following a suggestion of Charlie's, any member of the team who was responsible for a design goof agreed to buy one martini for all other members of the team at the end of the effort—one martini per goof, non-cancelling. On the day of reckoning we all repaired, of course, to the F&T. I can't remember how it all turned out.]

The Move to Washington University

The weeks immediately following our intensive summer effort did not go well. We were not only exhausted but were also confronted with an unanticipated organizational problem. The nascent M.I.T. Center, prospectively multi-institutional and multi-disciplinary, turned out to be irredeemably multi-problematical as well and de-materialized. The result was that once again the peripatetic LINC team found itself in need of a more suitable home for its work. We were ...um... disappointed.

I suppose that these days it is natural to expect a group in such circumstances to form a commercial company. The LINC team, however, had always been more academically than entrepreneurially inclined. In many subsequent months of searching, the principals traveled about the country and met with many university presidents and trustees, examining several propositions quite seriously. But it was an unscheduled meeting in Cambridge with George Pake that convinced us that the best choice for the continuation of the program was Washington University in St. Louis, where Dr. Pake was Provost in the years before he left the academic world to set up XEROX PARC. He had heard about our situation from Professor Cox, he said, and had "just happened" to be visiting Cambridge on his way to Woods Hole (he never got there). He had stopped by so that we could, in his words, look him over. We were already well acquainted with Jerry Cox, an old friend even then, especially since those final hectic days before summer, and had a high regard for his innovative work in biomedical computing at Washington University. For many of us, then, this extraordinary meeting with George Pake made an already very promising possibility irresistible.

And so it was that the Washington University Computer Research Laboratory was established in 1964 under the direction of William N. Papian, Associate Dean of Engineering. CRL set up shop in newly renovated space made available by its new-found "sister laboratory", the Biomedical Computer Laboratory under Jerry Cox. Tom Sandel accepted an appointment as Professor of Psychology, and I became Research Professor of Computer Science and Associate Director of CRL. Many from the Cambridge team, including Severo, Mishell, Howard and Ken Lewis, and Constance and Joe Towler uprooted and moved to St. Louis, followed by others from M.I.T. over the next few years. Charlie remained in Cambridge to complete both his military service and his doctorate at M.I.T. and rejoined the group a

year later as Associate Professor of Physiology and Biophysics. Norm Kinch rejoined us after an assignment at an experimental radar site operated by Lincoln Laboratory in the Southwest. Mary Allen received her appointment letter from George Pake midway in a one-year trip around the world (she was then in Calcutta), but before coming to St. Louis spent another year as an extramural member of CRL working on a new assembly-program/operating system, LAP4, using a LINC set up in the living room of her family home in Baltimore — surely a first in personal computing. But the original team never entirely regrouped. To our great regret, George Gerstein and Belmont decided that their immediate scientific interests were better served by accepting appointments at the University of Pennsylvania in the Laboratory of Dr. Britton Chance, and Bill Simon elected to accept an appointment at the Harvard Medical School.

Phase II Activities

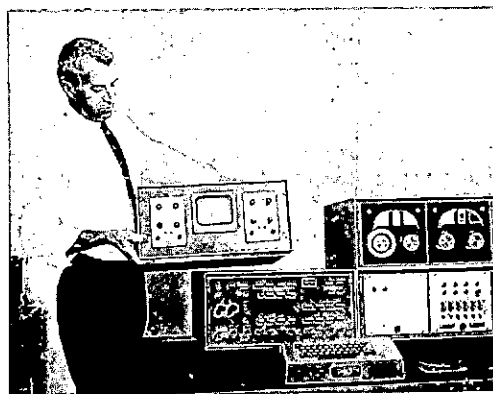
Four main tasks faced us in carrying out our Phase II responsibilities under the formal evaluation program.

- 1) We had to assure that the LINC equipment itself had been transplanted successfully into each of the participants' laboratories and was kept up-to-date.
- 2) We had to complete and distribute further documentation on the machine and its use.
- 3) We had to improve LINC software, starting with an enhanced version of the basic assembly program that provided automatic filing capabilities and improved editing and operational features.
- 4) Finally, we had to accumulate operating experience with the LINC in our own work in biomedical research and in other application areas.

Assuring ourselves and our sponsors that the LINC was taking root required considerable use of the telephone and post office as well as visits to each site. A few faulty switches and parts needed to be replaced, a few adjustments made, and a few circuit improvements installed as we verified their need. We adhered to the principle that any modification to one machine meant a modification to all machines. By and large, however, machine reliability was excellent, thanks to sound engineering by Charlie, Bill Simon, and Don Malpass as well as to the robustness of DEC circuit packages when carefully used. [From one of the sites, the only call for hardware help we ever got dealt with what to do about the fact that the elapsed-time meter on the power supply had just jammed at 99999.]

Completing a set of finished documents on LINC hardware and operation was more difficult (the evaluation program participants had been able to take away from Cambridge only the roughest of descriptive material and operating notes). Among other things, it meant that a full production version of a LINC kit and its accompanying assembly and test procedure documentation had to be checked out and certified. Not long after CRL had been set up, Mort Ruderman brought the first complete DEC-

produced kit to St. Louis. Mishell and Severo then put it together and verified the accuracy of the documents and test procedures, making a few necessary corrections. Final documents were prepared with the help of newcomers Dave Stewart (who had worked with Charlie during his Air Force days), Gerald Johns, Robert Ellis, and Maurice Pepper. After printing and distributing revised final documents to all evaluation program participants, we sold document sets at cost to anyone who wanted them.



(Top to bottom) The LINC kit produced by DEC; Mort Ruderman of DEC (left), Mishell (rear) and Severo assembling the kit; Norm Kinch stacks console modules.

Building up a base of operating software was accelerated with the help of the Biomedical Computer Laboratory. A variety of utility programs were written by our BCL colleagues Jerry Cox, Mike MacDonald, Sharon Davisson, and others. BCL incorporated these into LAP4 (an interim modification of the LINC Assembly Program, LAP3), and many of its operating features were later incorporated by Mary Allen in the ultimate version, LAP6. Software was generally distributed on LINC tape reels via the mails. Since direct exchange of programs among the participants was rare, we did what we could to certify and distribute copies of application software that was submitted to CRL or written at CRL or its sister laboratory BCL.

Use of the LINC in our own work was supplemented by work at BCL, where a few kits were assembled and used in connection with collaborative programs with the Washington University School of Medicine and its associated hospitals. Later we acquired several of the LINC variant machines made by DEC and others and began to use them in our developing research program in macromolecular systems (which soon took over as the major focus of CRL activities). [BCL went on to design the Programmed Console, the result of a design seminar that Jerry and I taught in 1965 [17]. Known as the PC, it provided both autonomous and remote-connection modes of operation and thus was one of the earliest "smart terminals". It was subsequently produced in small numbers and made available to radiologists for radiation treatment planning under a national program modeled after the LINC Evaluation Program.]

The Final Evaluation Program Meeting

The program participants began to use and then gradually depend on the LINC in their research. It had not seemed so, however, at our first re-gathering in June, 1964, when we all met for a show-and-tell at a distinguished old resort hotel in New Hampshire. Just short of a year since the Cambridge Summer, there hadn't yet been enough experience gained in the use of the new tool, especially in view of the scarcity of software and the upsetting problem of relocating the LINC core group. No one was greatly surprised. But at the final LINC Evaluation Program meeting in St. Louis in March, 1965, the participants were well prepared and had by then accomplished a great deal of scientific work. The studies reported covered a wide range of topics [18]. Some of them were:

Operant conditioning of pigeons and monkeys. [One series of experiments made use of a wonderful Lazy Susan holding a pigeon at each of four stations around its circumference, with indexing into data-collecting position, stimulus generation, and data analysis all provided by the LINC.]

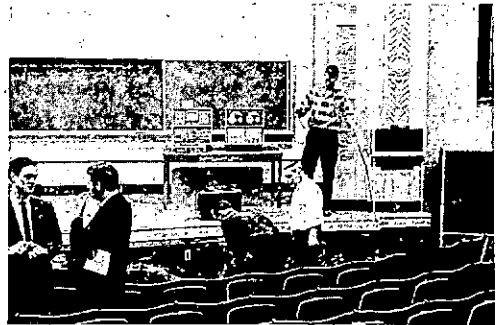
Spontaneous activity in thalamic and cortical neurons, behavior of single cochlear neurons, and somatosensory responses evoked in intracranial stimulation of cortex.

Pulsatile blood flow, cardiac muscle behavior, hydrodynamics of the mammalian

arterial system, and human finger tremor.

Genetics at the bacterial and molecular level using mass spectrometers and other instruments.

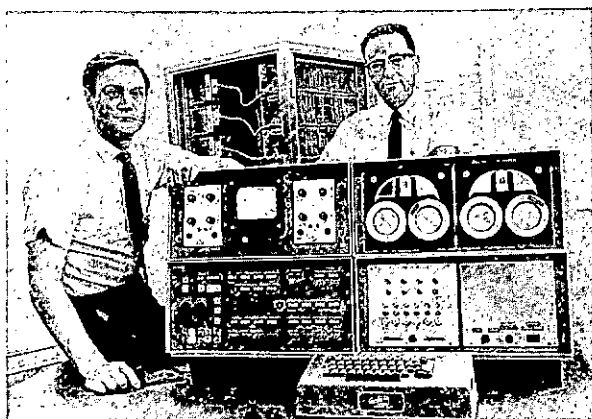
Communication between man and dolphin. [An unanticipated equipment hazard: the dolphin, one Elvar, could accurately spit a stream of seawater a distance of twenty feet.]



Preparation for the Final LINC Evaluation Program Meeting, March, 1965. (Top to bottom) I talk with Joseph Foley of Spear, Inc. while a LINC is being set up on stage; Prof. Harold Shipton (left) in discussion with Mort Ruderman and Winn Hindle of DEC; Drs. L. Wiencowski (left) and Bruce Waxman of NIH.

In addition to their scientific accomplishments the participants reported several other technical and software development activities. These included the connection of the LINC to computation center machines, the development of a system for remote control of the LINC, the design of interface circuits for control of a blue-format tape transport and other laboratory equipment, and the development of several experimental operating system programs and floating-point routines.

By the end of Phase II the Evaluation Program participants had an accumulated experience of about 50,000 hours of LINC use with remarkably little trouble, and at least that many hours had also been accumulated at other LINC sites with similar results. For the most part the original participants were awarded permanent custody of their machines following their reports of this strikingly successful operation in laboratories across the country.



(Upper) Tom Sandel and a now bearded Severo in a visit to the laboratory of Dr. G. S. Malindzak; visits were made by various members of the Washington University group to each of the participating Evaluation Program laboratories. (Lower) The author and William N. Papian with the final version of the LINC [Photo courtesy of the Saint Louis Post-Dispatch].

IN LATER YEARS

Although our formal responsibilities under the LINC Evaluation Program had been discharged, there was still work to be done that would take some of us a few more years.

Final LINC Modifications

Following the recommendation of the growing band of LINC users as reported at the final Evaluation Program meeting in St. Louis, a decision was made to undertake a number of hardware modifications. A new register and an arithmetic overflow circuit were provided to extend the range of arithmetic and to facilitate running a "certified" floating-point software package for which a considerable consensus had developed among the mathematically inclined. These changes were seasoned, documented, and distributed (with a few installation visits) to all of the original LINC sites, as was the floating-point package itself. Similarly, data and program interrupt features were incorporated to improve performance in several high rate applications. Altogether six new instructions dealing with these new features were wired into all machines.

The Final LINC Operating System

The final assembler/operating system, LAP6, was put together by Mary Allen with great care. Discussion of its specification had begun early in 1965 during her visits to several of the participating laboratories to develop a consensus regarding users' needs. A decision to double the initial 1K memory size had already been made; but as Mary Allen put it, doubling a 1K memory produces another small memory. Despite this limitation she was able to define a remarkably efficient operating system based on a LINC tape scrolling algorithm developed by Mishell and Severo. LAP6 included a line-by-line editor, an assembler, automatic management of files, user-defined metacommands, and runtime debugging aids [19]. It was thoroughly tested before being distributed in 1967 and the accompanying LAP6 Handbook still stands as a model of simplicity, accuracy, and usability [20]. A student of philosophy (today a lawyer in Massachusetts), Mary Allen quoted Kierkegaard in the foreword to the handbook:

To promise the System is a serious thing.

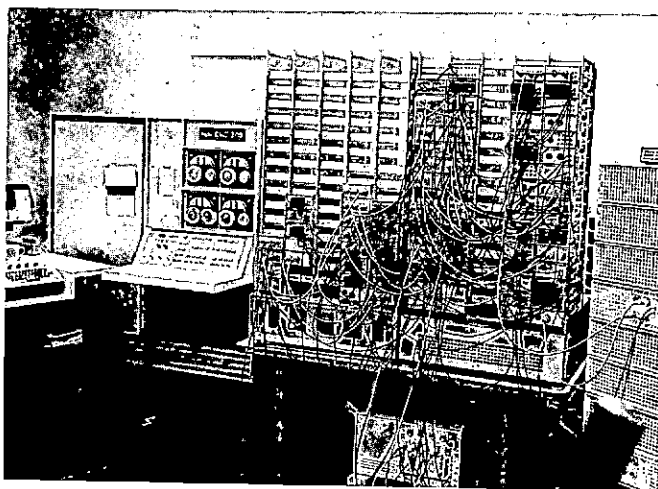
The handbook and the second edition of its companion programming tutorial document published in 1969 reflect the final form of what is now referred to as the "classic" LINC [21].

Manufacture of the LINC and LINC Variants

DEC went on to manufacture altogether fifty or sixty classic LINC's, only a few of these in kit form—an idea whose time never quite came. [Some of the kits were assembled for others by Prof. Harold Shipton of the State University of Iowa, previously a member of the LINC Evaluation Board. "Shippy", one of the most charming people ever to walk the face of the planet and well known to the biomedical community for his perceptive and imaginative engineering, later joined the faculty of Washington University.]

In 1965 I joined forces with Dick Clayton of DEC to design the LINC-8, a 32K dual-machine combination of the LINC and Gordon Bell's PDP-8, in which the complex LINC tape control logic was relegated to a concurrently executable program on the PDP-8 side using software written by Severo. While the nearly 150 LINC-8s were being made, Dick designed a new version of the machine, the PDP-12, of which about 1000 were manufactured [3].

In 1965 a new Massachusetts start-up company, Spear Inc., made its appearance. It began to manufacture a 4K integrated circuit version of the LINC, called the micro-LINC 1. Spear went on to produce the micro-LINC 300, a higher-performance 32K variant. [Spear, Inc. subsequently became a division of Becton Dickinson and Company. I have no doubt that the transaction helped Spear's former president farther along toward his life-long goal of retiring to some small South Sea Island that had an 18-hole golf course and a native monarch.]



A Spear Inc. micro-LINC 300 (left) providing operational support to an experimental macromodular system at Washington University.

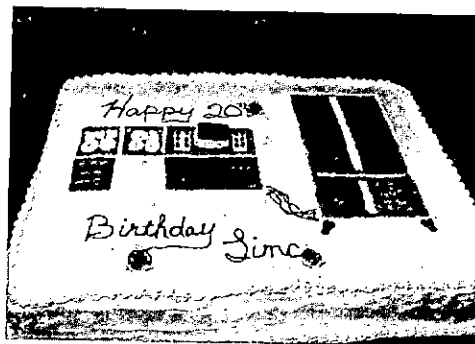
DENOUEMENT

With more than 1200 LINC or LINC variants at work around the world, research over the ensuing years began to result in very substantial contributions to the body of scientific literature. An effort was made to maintain a bibliography of LINC-related publications for the first few years, but the task soon got out of hand. The July, 1969 edition lists more than 150 scientific papers, journal articles, and published books [22]. By then the growth rate of bibliographic references was already doubling each year, and the number of LINC programs and application notes alone soon became so large that responsibility for handling them had to be turned over to the DECUS Program Library.

The careers and lives of those associated with the LINC development continued to grow and change in many ways, as new academic appointments were assumed and new professional challenges undertaken. Many early students of these scientists and engineers, and their students in turn, went forth to seek their fortunes after training in the LINC and its ways.

Washington University's program in the medical and biological research uses of computer science and technology grew in prominence and soon came to be regarded among the foremost in the country. In the course of years Prof. Jerome R. Cox became Chairman of the Department of Computer Science, and Prof. Charles E. Molnar, Director of the Institute of Biomedical Computing. Dean William N. Papian retired from the University to private consulting practice, as did I. In a very saddening turn of the historical wheel Prof. Thomas T. Sandel, after many years as Chairman of the Washington University Department of Psychology, died just weeks before the LINC's twentieth anniversary gathering of old friends of the Summer of '63 was to take place.

The LINC design went on to influence the design of DEC machines that further reinforced the concept of the small computer as a tool for personal work and very soon took over center stage. Yet over the years the LINC and its variants continued to serve the needs of biomedical research. A few of them were still on the job productively in 1985, and one of these—perhaps the last of the "classics"—could be found at the Massachusetts General Hospital, not yet retired after more than two decades of continuous use.



The birthday cake that made its appearance at the LINC Twentieth Anniversary Celebration held on November 30, 1983 at NIH.

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APPENDIX

The LINC Evaluation Program Participants

Without any doubt whatsoever, as Tom Sandel would have said, the success of the LINC is due in incalculably large part to the pioneering work of the evaluation program participants. Its formal members were: Drs. E. O. Attinger and A. Anne, Research Institute, Philadelphia Presbyterian Hospital; Dr. D. S. Blough, Dept. of Psychology, Brown University; Drs. S. Goldring and J. L. O'Leary, Dept. of Neurology, Washington University; Drs. F. S. Grodins and J. E. Randall, Dept. of Physiology, Northwestern University; Drs. J. E. Hind and C. D. Geisler, Laboratory of Neurophysiology, University of Wisconsin; Dr. J. Lederberg and Lee Hundley, Dept. of Genetics, Stanford University; Dr. C. A. Boneau, Dept. of Psychology, Duke University; Dr. J. C. Lilly, Communication Research Institute; Drs. G. S. Malindzak and F. S. Thurstone, Dept. of Physiology, Bowman-Gray School of Medicine; Drs. G. F. Poggio, G. Werner, and V. B. Mountcastle, Dept. of Physiology, and Dr. B. Weiss, Dept. of Pharmacology and Experimental Therapeutics, Johns Hopkins University; and Drs. J. W. Woodbury and A. M. Gordon, Dept. of Physiology, University of Washington.

The number of LINC's actually built in the summer of 1963 was about twenty. Several other investigators had been invited to participate on an informal basis. These informal participants assembled their computers alongside the others, using their own funds but taking advantage of whatever batch orders were placed for parts and subassemblies. They were: Drs. K. Killam and A. J. Hance, Dept. of Pharmacology, Stanford University; Dr. H. E. Tompkins and Mr. J. S. Bryan, National Institutes of Health; Dr. J. B. Lewis, M.I.T. Lincoln Laboratory; and Drs. R. Stacy and N. Bell, Institute of Statistics, North Carolina State College.

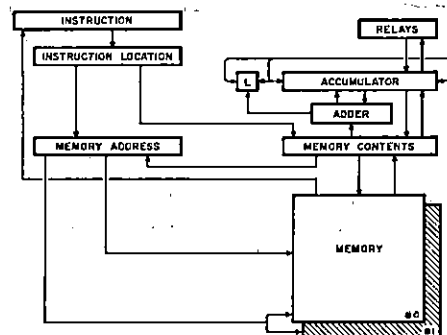
Under the chairmanship of Dr. T. T. Sandel of

M.I.T., the LINC Evaluation Board included Dr. M. A. B. Brazier of the University of California at Los Angeles, Dr. J. R. Cox of Washington University, Dr. E. R. Dempster of the University of California, Dr. J. Macy, Jr., of the Albert Einstein School of Medicine, Dr. H. V. Pipberger of the Veterans Administration, Dr. M. D. Rosenberg of the Rockefeller Institute, and Prof. H. W. Shipton of the State University of Iowa.

THE EVALUATION PROGRAM LINC INSTRUCTION SET

FULL ADDRESS CLASS	
	ADD X
The right-most ten bits of the instruction word specify one of the memory registers 0-1777 (octal).	
ADD X	Add the contents of memory register X to the Accumulator.
STC X	Store the contents of the Accumulator in memory register X, and clear the Accumulator.
JMP X	Take the next instruction from memory register X, and save the sub-routine return point in memory register 0.

INDEX CLASS	
	LDA $i \beta$ LDA $i 0$
OPERAND OR ADDRESS	
If $\beta \neq 0$, the instruction is single word length and the address of the memory operand is located in index register β ($1 \leq \beta \leq 17$ octal). If $\beta = 0$, the instruction is double word length and the second word is either the operand (case $i = 1$) or the address of operand (case $i = 0$). The specified index register is incremented by ONE before use if $i = 1$.	
LDA $i \beta$	Load the Accumulator with the memory operand.
STA $i \beta$	Store the contents of the Accumulator in the specified memory location.
ADA $i \beta$	Add the memory operand to the contents of the Accumulator.
ADM $i \beta$	Add the memory operand to the contents of the Accumulator and leave the sum in the Accumulator and in the memory operand location.
LAM $i \beta$	Add the memory operand to the contents of the Accumulator, together with any previous overflow held in the Link Bit. Leave the sum in the Accumulator and the memory operand location, and retain any new overflow in the Link Bit.
MUL $i \beta$	Multiply the contents of the Accumulator by the memory operand, and retain either high-order half or low-order half of the double-length product in the Accumulator.
SAE $i \beta$	Compare the contents of the Accumulator with the memory operand, and skip the next instruction if they are identical.
SRO $i \beta$	Rotate the memory operand to the right one place and skip the next instruction if the sign bit of the operand is ZERO.
BCL $i \beta$	Clear each bit in the Accumulator which corresponds to a ONE in the memory operand.
BSE $i \beta$	Set to ONE each bit in the Accumulator which corresponds to a ONE in the memory operand.
BCO $i \beta$	Complement each bit in the Accumulator which corresponds to a ONE in the memory operand.
DSC $i \beta$	Display character intensifying points on the scope in a 2 by 6 array according to the bit pattern of the memory operand.



HALF-WORD CLASS	
	LDH $i \beta$ LDH $i 0$
OPERAND OR ADDRESS	
Addressing is similar to that of the INDEX CLASS, except that the left-most bit of the address specifies which half of the memory operand is used. When $i = 1$ and $1 \leq \beta \leq 17$ (octal), the address word in index register β is incremented before use, in such a way as to step through consecutive half-words, the address of the operand increasing by one on every second reference.	
LDH $i \beta$	Load the Accumulator with the specified half of the memory operand.
STH $i \beta$	Replace the specified half of the memory operand with the contents of the right half of the Accumulator.
SHD $i \beta$	If the contents of the right half of the Accumulator are not identical to the specified half of the memory operand, skip the following instruction.

TAPE CLASS	
	(MTP) $i u$ RDC
SECTOR BLOCK NUMBER	
These are double word length instructions in which the first word specifies the tape unit (u -bit), the motion state following execution (if $i = 0$, the selected unit is stopped), and in which the second word specifies one of eight sectors of memory and one of 512 tape blocks between which transfers are to be made. All required searching operations and checking are performed automatically, and are repeated if checks indicate improper transfer.	
RDC $i u$ Q, N	Read tape block N into memory sector Q, and check the transfer.
RCG $i u$ Q, N	Read from one to eight consecutive tape blocks, beginning with block N, into memory and check all transfers.
RDE $i u$ Q, N	Read tape block N into memory sector Q.
MTB $i u$ Q, N	Move toward tape block N on specified unit.
WRC $i u$ Q, N	Write contents of memory sector Q in tape block N and check the transfer.
WCG $i u$ Q, N	Write from one to eight consecutive memory sectors on tape, beginning with block N, and check all transfers.
WRI $i u$ Q, N	Write contents of memory sector Q in tape block N.
CHK $i u$ Q, N	Find tape block N and leave the check sum for this block N in the Accumulator.

SHIFT CLASS		ROL		i	n
If $i = 1$, the Link Bit is coupled into the shift path. $0 \leq n \leq 17$ (octal)					
ROL $i \ n$	Rotate the contents of the Accumulator n places to the left.				
ROR $i \ n$	Rotate the contents of the Accumulator n places to the right.				
SCR $i \ n$	Multiply the contents of the Accumulator by 2^{-n} .				

SKIP CLASS		SNS		<i>i</i>	<i>n</i>
Skip the next instruction if the specified conditions are met. If <i>i</i> = 1, the skip conditions are reversed.					
SNS <i>i n</i>	Check whether Sense Switch <i>n</i> is up, $0 \leq n \leq 5$.				
AZE <i>i</i>	Check whether the Accumulator contains ZERO.				
APO <i>i</i>	Check whether the contents of the Accumulator are positive.				
IBZ <i>i</i>	Check whether either tape unit is reading an interblock zone mark.				
SXL <i>i n</i>	Check whether External Level input line <i>n</i> is negative, $0 \leq n \leq 14$ (octal).				
KST <i>i</i>	Check whether a key has been struck on the keyboard.				
LZE <i>i</i>	Check whether the Link Bit contains ZERO.				

SET	SET		i	β
	OPERAND OR ADDRESS			
SET $i \ \beta$	Set register β , $0 \leq \beta \leq 17$ (octal), to the value of the second word (case $i = 1$) or to the value of the operand whose address is located in the second word (case $i = 0$).			

DISPLAY		DIS		i	β
DIS	$i \ \beta$	Intensify a point on the scope whose vertical position is given by the right-most nine bits of the Accumulator and whose horizontal position by the right-most nine bits of memory register β , $0 \leq \beta \leq 17$ (octal). If $i = 1$, increment contents of register β before use.			

INDEX AND SKIP		XSK		i	β
XSK	$i \ \beta$	Increment by 1 the contents of memory register β (if $i = 1$) and skip the next instruction if the new contents of this register equal 1777, 3777, 5777, or 7777 (octal).			

SAMPLE	SAM		i	n
SAM $i \ n$	Convert the analog signal appearing on channel n , $0 \leq n \leq 17$ (octal), to an eight-bit binary number in the Accumulator. If $i = 0$, this instruction takes 24 microseconds; if $i = 1$, the instruction is completed in 8 microseconds although the conversion process continues for an additional 16 microseconds.			

MISCELLANEOUS		HLT
HLT	Halt the computer and sound a gong.	
CLR	Clear the Accumulator and Link Bit.	
ATR	Load the six Relay flip flops from the right half of the Accumulator.	
RTA	Load the Accumulator from the six Relay flip flops.	
NOP	Do nothing for 8 microseconds.	
COM	Complement the Accumulator.	

OPERATE CLASS

OPR

i

n

These instructions form a general input-output command set whose execution is partially controlled by externally generated signals. Some functions of this instruction set are summarized below.

1. *Pausing*, with conditional restarting.
2. *Generating outputs* on any one of sixteen control output lines.
3. *Reading into the Accumulator* from either of two twelve-bit parallel sets of gates.
4. *Reading into the Memory Buffer* from either of two twelve-bit sets of gates.
5. *Clearing of A* conditional upon externally generated signals.
6. *Gating outputs* from the Accumulator to external equipment.
7. *Transferring information* from the Memory Buffer to the Accumulator under the control of external signals.
8. *Controlling high-rate inputs and outputs* between internal core memory and external equipment.
9. *Reading of keyboard*.
10. *Reading of console switches*.

The UCLA Brain Research Institute Data Processing Laboratory

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Historical Background

The Brain Research Institute is an interdisciplinary research unit of the UCLA Medical School, supporting basic research in fields which contribute to an understanding of brain mechanisms and behavior. In 1960 the School of Medicine was relatively young, having graduated its first class in 1955. Among the early professors to affiliate with the new medical school was Dr. H. W. Magoun, whose own research interests were in the nervous system. Under his leadership, a formal proposal was prepared requesting the University of California to establish a Brain Research Institute (BRI). The proposal was approved in December 1959 and by mid-1961, sixty-seven members from fourteen University departments (12 in the Medical School) moved into a new BRI building contiguous with the Medical School, and the Neuropsychiatric Institute.

When the Brain Research Institute at UCLA was planned in the mid 50's, very few scientists of any discipline recognized the potential of automated data processing as a research tool, and the use of computers by neurophysiologists seemed like science fiction. Dr. Ross Adey, a physician, professor of anatomy, and a ham radio operator, understood the potential of the computer. Adey convinced Magoun and Dr. Jack French, the BRI's new director, that the computer revolution would bring enormous changes to neurophysiology. In 1960, the Institute made a commitment to obtain funding from NIH to pursue computing research, and I was the electrical engineer who wrote the engineering

aspects of our proposal: to establish a Data Processing Laboratory whose major focus was the design and installation of a small general purpose computer facility centered around an automated analog-digital conversion center. By the time the Institute officially opened in 1961, the BRI was awaiting funding from the Institute of Neurological Diseases and Blindness (NINDB) for its successful grant application, "The Application of Computing Techniques to Brain Function," to develop new computer methods for treating data derived from brain study. This was the first support of computer research that NINDB had funded, and there was much controversy at NIH over the size of the grant, which was about \$290,000.

The goal of the grant was to introduce computing techniques to analyze electrical activity recorded from nervous structures in a variety of living forms ranging from invertebrate to man. The BRI had ninety projects and in over half of the laboratories, electrical signals of nervous activity were observed and recorded. Electrical activity recorded from nervous tissue was classified as "spikes" or "waves". The term "spike" referred to the fast electrical action potentials of discharging nerve cells, called neurons. "Waves" were slow rhythmic potential changes as seen in the electroencephalogram (EEG) which represented on-going oscillations from the brain. The goals of investigators studying these signals were varied, and included; relating electrical events in single nerve fibers to the physio-chemical processes that occur in the transmission of the nerve signal; monitoring electrical events in order to map pathways in the nervous system; correlating EEG changes in electrical activity with different behavioral or physiological states; classifying characteristic EEG patterns for clinical diagnosis; and monitoring electrical activity during different stages of sleep, conditioning or learning - to cite a few. All of these experiments were characterized by great masses of data which were largely assessed by the naked eye. The digital computer

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could provide a powerful tool for neurophysiologists to study these phenomena, but the incompatibility between the continuously time-variant nature of these physiological quantities and the discrete character code of the digital computer were major obstacles. Our immediate aim in designing the laboratory was to provide a facility to computerize the collection, editing, and processing of these data.

The newly formed Data Processing Laboratory of the Brain Research Institute was specifically designed to make the latest high speed computing techniques available in the BRI. But an analog to digital conversion system was needed to bridge the gap. In 1961, to make use of digital computers, the recorded analog data had to be digitized and stored on digital magnetic tape in computer readable format. We decided to make several analog magnetic tape recorders available for lending to individual laboratories, and to have a central facility, in DPL, with a versatile conversion system able to produce data tapes in IBM format. We wanted to enable our investigators to utilize the very advanced computing facilities available to the UCLA community at the time. We also planned to equip a small digital techniques laboratory to develop special purpose devices to investigate digitizing data at the source, and to implement the remote transmission of data stored on digital magnetic tape, between laboratories and computers. Additionally, we decided to rent a small general purpose computer and investigate the application of "on line" computing techniques to neuro-physiological data.

UCLA has had a long and established history in the field of computing, dating back to 1949 when the National Bureau of Standards supported design and construction of the Standard's Western Automatic Computer (SWAC) electronic digital equipment on campus (which continued in service until 1966). In 1956 the Western Data Processing Center was created under the joint sponsorship of the University and the International Business Machines Corporation (IBM). A 709 computer was installed in the Graduate School of Management to support research and education in the application of computing to business management. In the same period, the School of Engineering and the Department of Mathematics recruited Dr. Gerald Estrin to initiate a computer engineering program and to help expand scientific computing at UCLA. With the aid of a grant from the National Science Foundation the University established the Campus Computing Facility in 1961. In fact, in 1961, three IBM 7090 computers arrived at UCLA: one for the Western Data Processing Center, one for the Campus Computing Center, and one for a new

Health Science Computing Center. Dr. Wilfred J. Dixon, Professor of Biostatistics in the Medical Center, had also obtained support from NIH for computation on medical data, and obtained a large mainframe to be housed in the Medical School. These three computers attracted the attention of the Defense Advanced Research Project Agency (DARPA) and generated the early research that led to the now famous ARPA network. I recall from conversations with Dr. Dixon that the campus mainframe-providers were very disturbed by the vast quantities of input and output data the biologists and medical people used. They believed that only small amounts of input or output data were required by scientists, assuming that the computer's speed and sophistication made appropriate use of clever algorithms. This was just prior to business applications of high speed computers, and most physical scientists believed at that time that the medical people were asking the wrong questions or did not have a discipline that was suitable for computation!

In 1960/61, the largest laboratory in the BRI was the Space Biology Laboratory (SBL), which pioneered the development of data acquisition and computing techniques. SBL programs planned to study the effects of environmental stresses, likely to be encountered in space flight, on the brain mechanisms of animals and man. In addition to having written the neurophysiological sections of the DPL grant to NIH, Dr. Adey also obtained support from the Air Force and the National Aeronautics and Space Administration to establish SBL for studying information storage mechanisms in brain systems tested under conditions of simulated ballistic flight. A major segment of the SBL program studied the electrophysiological correlates of behavior by means of electrodes implanted chronically in normal behaving animals. Dr. Adey's aim was to find the EEG relationship to behavioral states of wakefulness, alertness, and decision making. The Data Processing Laboratory was designated as the computation center to support activities of the SBL staff.

In 1961, another new program for the BRI was the Clinical Neurophysiology Unit. On a mandate from Congress, NIH had set up a program designed to support facilities in which the techniques of basic research could be applied to clinical practice. In response, the National Institute of Neurological Diseases and Blindness funded the BRI to investigate basic neurophysiological methods suitable for human patients who could receive therapeutic intervention in the nervous system for temporal lobe epilepsy. In this program the techniques of basic neurophysiology, as developed in animal experimentation, were used to study patients with

neurological and psychiatric disorders. There was particular interest in correlating recordings obtained from electrodes placed on the skull of patients, with activity recorded from the cortex and deep brain structures. An operating theater, ten bed suite, electrophysiological recording unit, and the basic facilities of the Brain Research Institute were made available. In particular, the computerization of patient records would make possible studies of implanted electrodes from human patients by Dr. Mary A. B. Brazier, who had joined the BRI at that time. Dr. Brazier had been an electroencephalographer at the Massachusetts General Hospital, and had frequent contact with her colleagues at MIT. In the early days of DPL we had frequent visits with members of the Communications Biophysics Group of the MIT Research Laboratory of Electronics (1, 2).

DPL was the first integrated electronic and computer laboratory established for the express purpose of developing automated technology for nervous system research. DPL was designed to be a resource for the conception and implementation of new computer based methods by neurophysiologists and engineers in the BRI. I was driven by the need to make computer systems easier to use by medical scientists, rather than by "hacker" motivation; i.e. the need to program computers in the most clever or economical way possible. I wanted to bring computer technology to bear on the problems of neurophysiology and wanted a DPL that would enable experimenters to gain research strength and perspective from the large computing installations on our campus. This approach to computing systems was rare in 1960 and stemmed from my engineering education in which I was sensitized to a systems engineering approach to problem solving. Of course, the problem of asking meaningful neurophysiological questions still remained, and I was very dependent on my physiological colleagues.

My personal interest in brain waves stemmed from my position as an electrical engineer in the electroencephalographic department of the Neurological Institute in New York City in 1951. I had just received my Ph.D. in electrical engineering from the University of Wisconsin and my husband had obtained his Ph.D. in 1950. He was employed at the Institute for Advanced Study (IAS) in Princeton on the Electronic Computer Project. I also worked on the IAS computer project for several months, but sought a position in my own specialty. I had trouble obtaining traditional employment as an electrical engineer because my commitment was not taken seriously; a common attitude towards women's careers in the 50's. During

my graduate days at Wisconsin, I had heard a talk about the electroencephalogram and believed that the study of this electrical phenomenon should be of interest to an electrical engineer. One of the compensations for the daily four hour commute between my home in Princeton, N.J., and my work in New York City, was being able to participate in the social and intellectual life of the Institute for Advanced Study (IAS) where the computing machine, called the Johniac, was being built under the leadership of John von Neumann. Frequently we went out to dinner with the von Neumanns, and Johnny, as everyone called him, always queried me about the status of my EEG research. Johnny's interest in the brain stemmed from his interest in automata. In 1954 we had the opportunity to go to Israel to build a version of the Johniac at the Weizmann Institute of Science, where my computer experience continued (3).

While employed at the Neurological Institute in 1951, I redesigned an electronic frequency analyzer for bioelectric signals. The frustrations of adjusting analog filter circuits in the early 50's, coupled with my new experiences in digital logic design, put me in a good position to introduce electronic digital techniques for recording the impulse firing pattern of neurons in 1960 (4). Consequently, I became involved with the use of computers by the neurophysiological community, and joined the BRI in 1960. When the NINDB awarded the Brain Research Institute our first computer grant, it included funding for my proposal: to design and implement an analog to digital conversion system for DPL. This system had the versatility to digitize both ongoing electrical activity amplitudes and the time interval between neuronal discharges. Both EEG and spike train investigators could make analog data tapes to format into IBM digital tapes for analysis at the Health Science Computing Facility. The facilities and capabilities of the DPL in the early 60's are described in reference (5). Renewals of this grant by NINDB provided 18 years of continuous support and enabled DPL to consistently remain a leader in the development of computer methods for neurophysiological research.

During the years 1960-1975, the period covered by this conference, DPL made pioneering contributions in the areas of: analog to digital conversion; automated data acquisition and preprocessing; signal analysis, interactive graphics, modeling and simulation, laboratory computer systems, and distributed processing systems. Throughout those years, over 100 investigators consulted with DPL staff on the introduction of computing techniques, and DPL activities contributed to the computer awareness of many more.

During this period, nervous system research evolved from a fragmented quantitative descriptive discipline to an interdisciplinary neuroscience. In the next paragraphs, I will elaborate further on the type of computing system research done in the BRI-DPL during the three five-year periods between 1960 and 1975. In my review, I will not dwell on the computer technology of the system, details of which can be found in my references. The neurophysiological questions addressed by BRI investigators, and the role of computers as a tool in seeking answers, can be reviewed in the BRI Annual Reports (6). A brief overview of the major advancements of the laboratory follows.

1960-1965: Analog-Digital Conversion

The first high speed analog-digital conversion system on the UCLA campus was housed in DPL. In 1961, we purchased an analog-digital (A-D) conversion unit, built by the Airborne Instruments Laboratory, to meet DPL design specifications. Our original choice was to rent a computer from the Digital Equipment Corporation, because of DEC's ability to input analog data. But DEC would not rent equipment, and our budget did not allow us to purchase. Our conversion system included an analog tape playback unit, the 16 channel A-D multiplexer and converter, a storage unit, and a digital output tape, all integrated into a system by DPL staff. A storage device was necessary to hold data read from an analog tape, as the digital tape was stopped and started to prepare the spaces and format required by logical records and files. We decided to use a small computer as the storage device, because a computer both controlled data flow and ran computer programs. We rented a Control Data Corporation 160a which provided the mass storage to allow the timing and tape format required for IBM-compatible digital tapes which we processed on the Health Sciences 7090. In a typical off-line operation, the computer controlled a tape-to-tape conversion system by sampling and quantifying information recorded on analog magnetic tape and assembling it into a series of IBM characters which were recorded 200 bits per inch on digital magnetic tape. To digitize the analog data properly, rules of sampling theory were observed involving appropriate regard for the frequency spectrum of the original data, and the information to be extracted. These factors dictated such converter requirements as sampling rate, sampling aperture and quantization level. A control unit supplied the timing and control signals and the logic that provided the system with flexibility to handle either EEG or spike electrical activity. (7)

The system was designed to serve the needs of many investigators employing different data acquisition methods and assumed that suitable record and play-back equipment existed to reproduce their recorded signals. There were three primary off-line modes of operation: for spectral analyses, averaging responses, and inter-spike interval computing. The spectral analysis mode was heavily used by programs for correlation and spectral analysis which were all done on the IBM 7090. The use of the power spectrum was introduced to the study of the electroencephalogram in 1962 by Dr. Don Walter, a significant contributor to DPL throughout its history. EEG data typically covered frequencies from 3 to 40 cps, in the 20-100 microvolt range and was amplified by recording amplifiers. With the advent of the fast Fourier transform (FFT), devised by Cooley and Tukey (8), spectral calculations became quicker and easier, and became used extensively in studying the structure of EEG data (9, 10). The measures which we normally calculated were the autospectrum, cross-spectrum (both amplitude and phase), and coherence. These measures allowed estimates of the distribution of power or variance as a function of frequency and of the interrelationships of activity in given frequency bands among different signals to be assessed.

The small memory size and relatively slow speed of the CDC 160a was a limiting factor for spectral problems which required very high-speed computing, but the computer was programmed to operate in an on-line fashion for average response calculations or for microelectrode studies. Microelectrode techniques recorded electrical activity from single nerve cells surrounding the electrode. The difference in recorded amplitudes of pulses in a spike train were the basis for discriminating between several discharging neurons recorded by the same electrode. These "spike" signals were in the millivolt range and required a frequency response to 30 kc/s to reproduce accurately their waveshape; however, bandwidths of 5 or 10 kc/s were sufficient to extract information as to firing pattern. It had been hypothesized that the temporal distribution of spikes represented a coding of information. Precise information on how nerves conducted signals had come from microelectrode studies in the peripheral nervous system, where neurons increased their firing rate as a function of stimulus intensity. Microelectrode studies were also made from deep brain structures, the electrode were positioned by geometrical coordinates as with gross electrodes. It was of great interest to know whether the subtle variations in the response of brain cells to different modes of stimuli were the equivalent of some "coding" process, and much activity was

directed toward obtaining inter-spike interval histograms of the nerve discharge pattern.

By 1963, over twenty investigators used the laboratory on a regular basis for two shifts a day. At that time, Mr. Dan Brown, manager of the laboratory, suggested we change to a Scientific Data Systems 930 computer which had a built-in a/d conversion system; we followed his advice.

1965-1970: Intelligent Peripheral Processors

Due to increased demands on DPL by a growing number of investigators, a program of hardware expansion resulted in the replacement of the SDS 930 with 12,000 memory locations by an SDS 9300 computer with 32,000 words of memory. In the 1966/67 academic year, the Health Science Computing Facility also switched from an IBM 7090 to a 360-75. DPL staff designed and installed an adapter which permitted direct connection between the 360-75 and the SDS 9300, providing a 2-way high speed information path between the two computers. Of course, with each change of computer hardware, much additional software had to be written.

During this time period, "dumb" terminals as input and output devices of remote medium or large general purpose computers were increasing rapidly in the commercial world. However, the use of "intelligent processors" with their own degree of independent processing was still in the pioneering stage. DPL undertook three projects which required these intelligent devices as input and output to a larger mainframe: a hardware software system known as SLIP; an analog-digital system remotely situated from the 9300 computer; and an IMLAC graphics processor interfaced to the 7091 mainframe. In accordance with the philosophy that the greatest assistance a computer could offer to research was real-time processing, the DPL had been working to extend the accessibility of the computer directly into the user's laboratory. This required a method for providing input and output capability throughout the BRI. In pursuit of this objective, the DPL installed a central cable facility extending from the basement computer room to all 10 levels of the BRI. For users, their respective intelligent processing input or output device connected them to the large computer and they were unaffected by others who were simultaneously using the same large mainframe. During this period, and for the next decade, Mr. Lazlo Betyar and Mr. Lionel Rovner were in charge of software and hardware engineering design.

A Shared Laboratory Interpretive Processor (SLIP) was designed in DPL to retrieve, operate on, and view data on a storage scope via a hardware-software system patterned after the Culler-Fried On Line System, which was designed to provide a convenient and rapid means for human interaction with a large digital computer (11). Their system was useful for problems requiring repeated communication between user and computer, and was best suited for users who needed to experiment with different formulations, methods of solution, or various types of numerical analysis. The SLIP system extended the capability of Culler-Fried to control input-output devices, necessary for handling the large quantities of data generated by neurophysiological experiments. The hardware of SLIP consisted of a keyboard and storage scope referred to jointly as the console. From the users point of view, operations on the console proceeded as if each user had a machine containing a single accumulator able to handle 144 elements with each element able to represent a 24 binary-digit operand. Each of the 144 values of the accumulator could represent a different subroutine, or could be considered to be one vector with 144 components. (12,13). SLIP provided a rapid means of interaction with the 9300 computer system on a priority interrupt basis. By 1968, DPL had six SLIP consoles and three more were planned for additional neurophysiological laboratories. The system was intended to avoid the need for neurophysiologists to become programmers, and to encourage them to use the easier, data oriented, time shared SLIP system. These consoles offered the investigator the opportunity to modify analytic programs being applied to data and to create new options; in addition, they could be programmed to function as the entire input-output control point for an investigator's digitization, experiment control, data analysis, data editing, and graphics display.

The consoles and the cable system throughout the BRI could connect any laboratory to the medium sized computer in the DPL, and from the DPL to the new HSCF IBM 360-91 through a tie-line. Digitized data could be sent over the tie-line and subjected to spectral and discriminant analyses, with the results sent back to the 9300 where a graph of spectra or lists of discriminant results were displayed on a SLIP console. The SLIP console was very useful for investigators working with neuronal spike data. The conceptualization of bioelectric signals as stochastic processes provided an analytical framework for the investigation of hypotheses concerning both the generation of the observed signals and the inter-relationships between the multiple observed signals. Dr. Jose Segundo and his

collaborators created a flexible system for on-line analysis of neuronal spike trains, using the SLIP system, and applied it to their studies of aplysia to provide numerous forms of statistical analysis of specific trains and their relationships

With the new medium sized computer in the DPL, the possibility of time shared on-line use in the neurophysiological laboratory had become a reality. A unique feature of the SDS system at the time was its 16 channel priority interrupt system essential for the real-time, multi-user environment we were building. In mid-1965, the first remote analog-digital conversion system and a SLIP console was installed in the EEG laboratory of Dr. Brazier. Brain waves were digitized from patients in her laboratory and transmitted to the remote SDS computer eight floors below. Computed results were returned to the EEG laboratory and viewed on a storage scope. The use of the equipment was to initially convert analog EEG information to digital form for immediate transmission to the SDS 9300 and then to the HSCF IBM computer for spectral analysis. Graphic displays from these computers were returned to her laboratory. Another use was to transmit data for analysis on the 9300 and get statistical outputs related to average response computing, e.g., to obtain information on the influence of variance on the build-up of an average response (14).

In Figure 1, Curves A through D represent one typical computer display photographed from a 4" by 5" cathode ray tube. The figure displays the results of an experiment in which a human subject was flashed 150 times at 1 f/sec. Figure 1A exhibits the average response banded by the standard error of the mean computer for flashes 140-150. Figure 1B exhibits the amplitude distribution of the last ten flashes only. Figure 1C is the averaged evoked response, and 1D the amplitude distribution for 150 flashes where the standard error of the mean has become so small it was not resolvable.

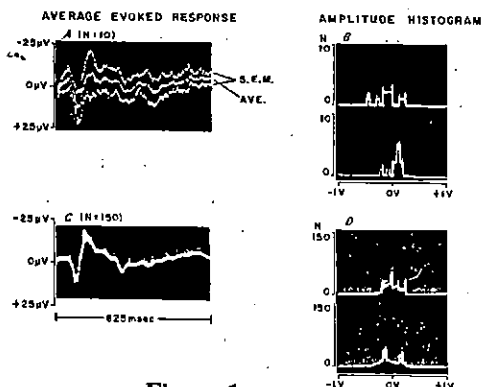


Figure 1

A third intelligent input-output device was the IMLAC graphics processor used to support a new technique to compute and display the electroencephalogram (EEG) as a spatial-temporal phenomenon. In this technique, a position on the screen of a cathode ray tube was congruent with a position in a recording array of electrodes on the subject's head. The potential distribution over the area of the head covered by the array was then computed and displayed as a contour map on the face of the tube. Succeeding displays represented distributions at successive instances of time and were photographed by a motion picture camera. The projected film recreated a time history of the potential field. In conventional electroencephalography, potential differences recorded between pairs of electrodes on the scalp were displayed as a parallel array of time functions, usually eight or sixteen traces at a time. Advances in analog-digital conversion, high-speed computing, and graphic display terminals enabled us to develop a new method for automatic computerized display of the EEG.

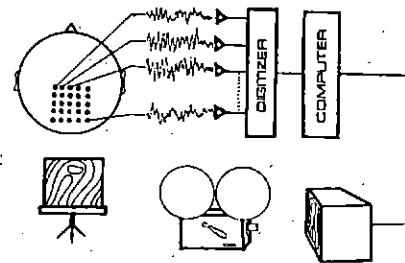


Figure 2

In Figure 2, the continuous electrical activity recorded by the electrode array was digitized and stored on magnetic tape. The digital tape data was interpolated by the computer to produce a contour map which represented, for one time instant, the potential distribution over the area of the head covered by the array. This map was displayed on a cathode ray tube and photographed under computer control. Figure 3 is an enlargement of five successive displays which represent the potential distributions at instances five milliseconds apart. The complete projected film, illustrated by the film screen in the lower left, recreates in slow motion the time history of the potential field (15).

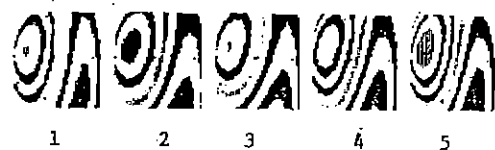


Figure 3

1970-1975: A Distributed Processors Network

By 1970, minicomputers were gaining popularity as a moderately priced computing machine. The DEC PDP-12 was available, and the PDP-11 was to be produced shortly. At the BRI, we realized that our time sharing system had become too costly to maintain. DPL had grown from two employees in 1961 to a staff of forty. We consulted with individual laboratories advising them to purchase new minicomputers if their computing needs required extensive hardware. For investigators whose computing needs only required analog-digital conversion, DPL planned to transport their activities to a night-shift off-line facility to produce IBM formatted digital tapes. At this time, NIH also cautioned the BRI that if our computing grant was to continue, DPL had to obtain a full-time director and become an interdisciplinary center with more emphasis on neurophysiological or medical goals. I was appointed director of the laboratory in 1970 and by the end of the year, the SDS 9300 computer had been removed and replaced by a PDP-12; three neurophysiological laboratories had also acquired PDP-12 computers.

Early in this period our Data Processing Laboratory interconnected three available computers: a DEC PDP-12 and an IMLAC PDS-1D in the DPL, and an IBM 360-91 in the HSCF to form a network of distributed processors for interactive graphics programs. This network utilized the strengths of each of the processors. The PDP-12 laboratory computer was well-suited for acquisition and preprocessing of neurophysiological data and for the generation of edited data sets. The IMLAC graphics terminal, with keyboard and light pen, provided a control processor for the transmission of edited data sets from the PDP-12 to the large scale IBM 360-91, and was also an interactive display terminal for the PDP-12 or the 360-91. The IMLAC had two instruction processors, one to control the display and the other a 16 bit minicomputer with a 4K word memory. The minicomputer controlled a serial communication interface which could link to a remote host by direct dial phone. The IMLAC PDP-12 interface design included a simplified scheme for I/O bus construction on the PDP-12 and a software system for assembling and loading IMLAC programs and brain map data for the PDP-12. An important application of this system, performed with Dr. R. I. Scabassi, was to facilitate the investigation of complex relationships between experimental and theoretical data in the spike activity of neurons (16). Dr. Ronald Harper was a neuroscientist who also joined our laboratory in 1971 and used this system extensively in a comprehensive sleep study on the sudden infant death syndrome.

Figure 4 illustrates the hardware of the three processor network utilized in our interactive graphics system.

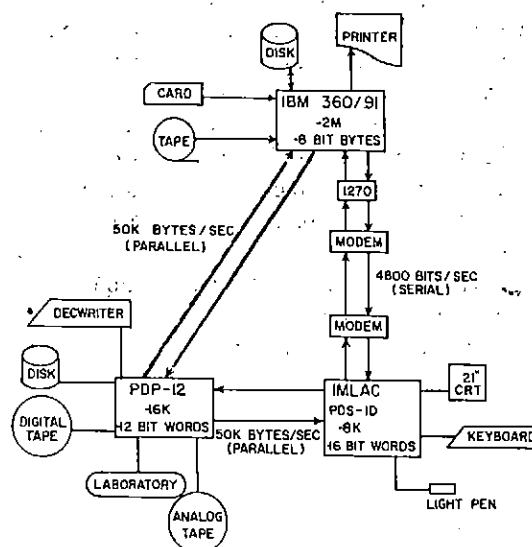


Figure 4

When I became the Director of the laboratory and PI on our NIH renewal, my personal research involved novel uses of interactive graphics as a tool for brain researchers. I worked with an innovative use of the network for a simulation program we called BRAINMAPS, to aid the surgeon-user of a stereotaxic device to determine the best trajectory for approaching a targeted brain structure. In the early 70's, CAT scanning had just emerged and NMR images were still far away. The use of computer-generated brain maps to combine diagnostic information from radiological scanning of a patient's head with general neuroanatomical information from brain atlases seemed like a useful idea. Brain atlases presented macroscopic cross-sectional maps of the human brain and provided indispensable localizing anatomical information to those neurosurgeons who used stereotaxic techniques. However, the large variability in the dimensions of human brain structures limited the usefulness of the standard atlas. Dr. Paul Crandall, neurosurgeon, did clinical research on partial epilepsies and stereotaxically implanted electrodes for chronic EEG recording to help lateralize the discharging focus. The purpose of the computer program was to develop a prototype to aid in the placement of multiple electrodes in the temporal lobe. Neuroanatomical maps, scaled for the individual patient, based on measurements obtained from his pneumoencephalogram, were used to provide stereotaxic coordinates. The recent introduction of computerized tomography made it possible to obtain the measurements required for stereotaxic surgery

without the injection of air as a contrast material. An interactive computer graphics system was implemented to scale and display brain maps, and a pilot study to evaluate its potential as an aid to better localization during stereotaxic placement was in progress. The system could serve the neurosurgeon by contracted or expanded standardized brain sections on the basis of x-ray data from the patient. During surgery the computer, by simulation, could monitor and display the position of the electrodes relative to neuronal structures as the array moved along a path to its ultimate site. Figure 5 is a Cal-Comp plot of thalamic region from the Schaltenbrand and Bailey Atlas (17). Neuroscientists also experimented with the system in their research with animal subjects (18).

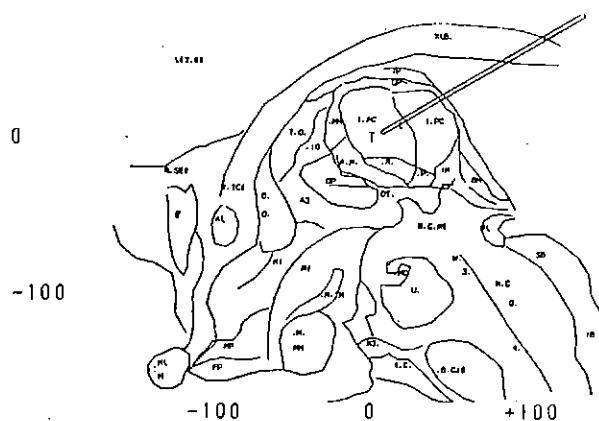


Figure 5

Another interactive application involved a computer network which was established between UCLA and the University of California at Davis for the purpose of gaining access to MUMPS, a popular computer language in the clinical medicine community. MUMPS is a multi-programming utility system developed at the Massachusetts General Hospital for medical applications; a MUMPS interpreter was part of the software supported by the Davis computing center and was not available through the computing centers at UCLA. Mr. Richard Buchness, a DPL programmer, required access to MUMPS in order to write a computer-aided instruction program for a pilot project on cancer education. We were able to complete the pilot program within several weeks because of our mini-network of distributed processors and the associated software which had been built by our programmers. Our use of MUMPS resulted in the only addition of a graphics capability to the MUMPS language which we knew about at that time. MUMPS could be used for interactive graphics when the graphics commands were encoded as character strings. The string manipulation features of MUMPS then allowed

graphics information to be handled like any other MUMPS string. A host-independent graphics program called "GRIP" ran on the IMLAC minicomputer. This program contained both an alpha-numeric scrolling editor and a graphics interpreter. The interpreter decoded specially framed graphics commands created by MUMPS subroutines at the remote host. We had a library of such routines for generation of points, lines, characters and beam position. Using this design, no modification of the MUMPS language was required to enable graphics programming for an IMLAC intelligent graphics terminal. The IMLAC terminal provided the user with vector and character generation, a light pen, and both alpha-numeric and function keyboards. We used the MUMPS interpreter running on the Burroughs B6700 at the UC Davis campus, 500 miles away. Our use of graphics was not limited to figures composed of points and line segments, but also included the presentation of items for selection in the form of menus, independent of the scrolling editor which could remain on the screen for any period. The user interacted with the menu via keyboard, function key, or light pen. Presenting lists of choices via menus as opposed to presenting successive displays increased the rate of flow of information between the user and the program (19).

Conclusion

Despite the significant "firsts" identified in this paper, the DPL ceased to function in 1979. Why? In 1979, DPL applied for an NIH renewal to institute a microcomputer network. Our grant was approved but not funded and we were encouraged to apply again. The computer research study section had been disbanded and our reviewers were primarily neuroscientists who did not understand microcomputers. The grant application refusal, coupled with the emergence of neurobiology as a central factor requiring BRI space caused us to give up our DPL housing. But perhaps most important, was the lack of recruitment of mathematically or computer oriented neuroscientists by the BRI. After most of our strong supporters had moved or retired, BRI did recruit first rate neuroscientists, however, their interest in computer research was minimal.

On a larger scale, the application of real-time computing for neuroscientists and medical diagnosticians is still in its infancy, though more than a quarter of a century has passed since DPL and its missions were organized. The lack of progress has been three-fold: financial costs, simplicity of use, and people's attitudes toward changing their methods of work. The past year has seen the personal workstation applied as a tool for all

intellectual personnel. The cost and ease of use have been significantly improved to meet market needs, thanks to the microprocessor and associated software. Users will have easier access to computer networks with increased power for data and program change, as well as immediate access to high speed visual displays, due to the emergence of portable graphics, supercomputers, standard software, and fiber optical devices for rapid transfer of data. Those scientists who use the computer as an indispensable tool for their research or practice will have a significant pay-off, and they will encourage other investigators to think in computer-structured terms. In the next quarter of a century the advances in neuroscience, cognitive science and artificial intelligence should make medical informatics a household term.

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THE HISTORY OF THE USE OF COMPUTERS
IN THE INTERPRETATION OF RADIOLOGICAL IMAGES

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INTRODUCTION

Throughout its history, diagnosis with a computer has been the target of the medical cartoonist, who displays humorous situations where the doctor, consulting his ridiculously large computer, gravely reports inappropriate diagnoses to his disbelieving patient. We laugh at this humor, yet, through lack of insight computers do make inappropriate diagnoses, and despite years of polishing, most diagnostic programs are still experimental in nature, and await a serious role in the diagnostic armamentarium.

Radiological diagnosis with a computer involves the development of complex models intended to simulate and improve upon human performance. There is a real need for such an effort since the frequency of human error in diagnostic decision making generally, and in the interpretation of x-ray images specifically, is astonishingly high (est. 20% detection, 10-50% diagnosis). (1) This high rate of error is largely unsuspected. Despite advances in imaging technologies with improved spatial, contrast and temporal resolution, a high rate of human error persists. A major element of this error lies in the failure of the reader to detect signs of disease which so often are embedded in a background of structured and statistical noise. The solution to this problem is complex and unresolved. Yet another source of error is in matching perceived sign information to the appropriate diagnostic classification.

In more than twenty-five years of trying to use a computer to improve upon human performance, I have had both suc-

cesses and failures. In this brief presentation today I will focus almost entirely on personal experiences in developing computer assisted interpretation of images, and how I came to be involved with computers in the first place. Also I will discuss some of the advantages and disadvantages of computer assisted interpretation, and where I think this technology will ultimately lead.

THE BEGINNING

In late 1946 I left the Army Medical Corps to find a residency in radiology. My hopes were to be accepted in the program at the University of Iowa, where as a medical student I was fascinated with the magic of making medical decisions from images, especially as performed by Professor Carl Gillies. However, I found that I was at the end of a long queue of applicants, and accepted instead the post of resident physician in pathology until the position of my choice became available in the summer of 1948. This detour proved to be very important to my future career, since pathologic anatomy was just the ticket for a better understanding of clinical radiology. My experience in pathology made me look good enough for me to be invited to join the academic staff when I had "completed my training". Parenthetically, even now I seem still to be completing my training; but then, the process entailed a fellowship at the Armed Forces Institute of Pathology in Washington, D.C., to last until I was formally appointed to my new position of Chief of the Radiological Services, VAH Iowa City. Arriving in Washington with my family, and waving a brand new certificate of The American Board of Radiology, I was greeted by my new chief, Col. William Thompson and by Dr. Aubrey O. Hampton, a distinguished radiologist then in private practice and consultant to the Registry of Radiologic Pathology. Having been asked to watch out for me, Dr. Hampton introduced me to Dr. Lent C. Johnson, Chief of the Registry of Orthopedic Pathology, who promptly put me to work on the task which has proved to be a consuming interest.

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Lent Johnson was an extraordinary pathologist. Brilliant, controversial, intuitive, intellectually organized, and unrestrained by the conventional thinking of his peers, Lent was highly respected by his friends and students. Lent's opinions about structure and process were exciting fare. A workaholic, he had integrated tumor histology and location with age and the physiology of bone growth into an exciting hypothesis on the origin of bone tumors, published as "A General Theory of Bone Tumors." (2) Lent was as skilled as any in the radiologic interpretation of bone disease, even though the state of knowledge of how to interpret x-rays of bone neoplasms was far from perfect. While a few signs such as "moth-eaten" and "Codman's triangle" were commonly used, their diagnostic and prognostic meanings were unknown. So it was agreed between Aubrey Hampton, Col. William Thompson and Lent Johnson that my mission would be to organize an exhibit which would display the radiological patterns of the common bone tumors correlated with gross and microscopic findings. At the fall 1951 meeting of the American Roentgen Ray Society our exhibit was awarded the bronze medal.

This modest success was not the end of my relationship with Lent Johnson. During our year of working together, too many unanswered questions had been asked, and too many issues were left unsettled, to leave either of us satisfied. We still did not know the meaning of the few radiological signs that had been described, and realized that the solution to developing this information was a detailed analysis of the radiologic images of a large collection where the outcome was known. The case material of the AFIP, while abundant, was of military origin where follow-up was difficult. The only collection of bone tumors we knew to have ample documentation and follow-up was The Bone Sarcoma Registry of the American College of Surgeons, then in residence at the University of Chicago. With my fellowship drawing to a close, I was anxious to begin the challenge of my new position. So, late in the fall of 1951, with an invitation to return to the AFIP at any time, I returned to Iowa City. In early 1954 I received a call from Dr. Johnson telling me of the news that the Codman Registry of more than 2000 primary bone tumors was now in file at the AFIP, and would I like to come to Washington to carry out the detailed analysis that we had dreamed of? With a three month leave of absence from the Veterans Administration, my reluctant wife and family saw me off to Washington to begin the most intensive work episode of my life.

MODELING THE IMAGE

At this point, the research goals were defined and the source of the data estab-

lished. Now began the task of building a model which would be used to extract the standardized clinical and radiographic data from each case in the Registry. The clinical data were relatively easy; they were numerical, consisting of months delay before diagnosis and length of survival after treatment. Kinds of treatment were also captured. I was to review the histologic material on each case in the context of the diagnostic summaries which had been recorded by such luminaries as Ewing, Codman and Phemister. Lent Johnson was to review atypical cases with me. The difficult part was to identify and decide which sign information should be included in the model. There we were exploring the unknown. I ultimately used a rather primitive consensus model which we had evolved to analyze the entire data set, and made a detailed pencil sketch of the x-ray of each tumor. Drawing images was tedious but led to my seeing the subtle changes in bone more clearly. With time it became apparent that the identity of the signs we had agreed upon fit less and less well with what I was seeing, and subconsciously I depended more heavily on sketching signs as an alternate way of recording information. This was no time to go back and change the model. My workday averaged sixteen hours, including weekends. Ultimately, the initial phase of this grueling task was completed and the data, with drawings and some copies of x-rays were packed in a large trunk which accompanied me to Iowa City.

Then began the analysis. Given that there were more than fifteen hundred cases with more than twenty radiographic variables for each, the length and numbers of summary sheets became impossible to manage. A better mechanism for data analysis was obviously necessary. It turned out that the United States Government was beginning to introduce machine record inventory controls into the VAH system, and I was given access to the IBM key punch machines for processing my data. Of necessity I became a semiexpert key punch operator, and personally encoded the data from each case on a single card. Now, developing composite survival characteristics for individual signs was easily possible.

The fibrosarcomas of bone were an especially valuable histologic type for sign and pattern analysis. Their radiographic patterns of bone destruction were a composite of the patterns seen in all histologic classes of tumors. Also, since fibrosarcoma has a paucity of tumor bone and of reactive response, which tend to obscure fine detail in radiographs, bone destruction was unusually clearly displayed. Experimenting, I separated cases of fibrosarcoma of bone into three data sets based upon one of three patterns (1) cystic destruction with sclerotic margins, (2) cystic destruction with ragged or

invasive margins, and (3) moth-eaten or permeated bone destruction. The five year survival statistics for these three groups were startling; 52% for the first group, intermediate for the second and 7.5% for the third! Equally startling were times for delay before diagnosis: nearly fifty months for the first group and six months for the third.

These results were exciting to both of us. Lent Johnson undertook to reorganize the basic structure of the model along lines which integrated pathology with the kinds of radiographic patterns, (location, size and shape; bone destruction; reactive new bone formation; and tumor bone.) I focussed on sharpening the identity and descriptions of the individual signs, and extending the collection of survival statistics. The drawings and duplicate copies of x-rays were essential to accomplishing this task. Periodically we met at the AFIP to compare notes and to iron out conceptual differences. New modeling concepts began to emerge. It was agreed that theoretically the model should be so complete that the encoded descriptors of a case should be sufficient to reconstruct the original image. This concept was tested with one of my residents (Dr. James Bauer) who sketched images from data I had encoded on several cases. His reconstructions were impressively similar to the original images. It was accepted that there were three basic patterns of bone destruction; geographic, moth-eaten, and permeated. The concept of analyzing for location, size and shape helped to implement several concepts of Johnson's general theory, especially those concerning the location of the tumor in relation to its histologic type. Size became a valued predictor. Since the time of this reorganization, the bone model has remained a stable yet dynamic concept; significant signs, such as burrowing in the presence of infection, are still being added.

Effective modeling of the radiographic image of a major disease class is a tedious iterative procedure, and is subject to many design errors. An especially troublesome error involved measurements, where instead of recording actual measurements, we broke up measurements into broad ranges, such as 1-4 cm., 4-8 cm., etc. In so doing, we lost our flexibility to determine the exact point at which a measurement became significant.

Now there was much to publish. However, Lent Johnson was a perfectionist, and unwilling to submit a manuscript for publication until he could see no possibility of further improvement. I, on the other hand, felt that I faced publishing or perishing, and with such a large investment of time and excellent results, was anxious to publish even in preliminary form. The extent of this conflict was such that it was never possible for us to pub-

lish any of our work together. Once, after I became professor and chairman at the

Because I considered the concept of modeling images so important and was unable to publish the bone model, I similarly modeled a collection of lung cancers provided by Professor Hans Ehrenhaft of the University of Iowa. This new model, applied to the lung cancer data base, replicated the success of the bone tumor model. (3,4) Presentations I later made on systematic analysis of bone tumors were published as chapters in a book (5,6). Finally, the details of the bone model were published in a monograph in 1971. (7) University of Missouri in 1956, I was so bold as to submit a manuscript under both of our names to a major radiological journal, which accepted it as a lead article. I later withdrew it at Dr. Johnson's insistence.

COMPUTER AIDED DIAGNOSIS FROM IMAGES

An important by-product of the bone tumor data analysis was the stack of Hollerith cards which held the encoded data from the Codman Registry. I analyzed the data on these cards in many different combinations in order to learn whatever I could about tumor behavior. Handling these cards was a regular event, and quite coincidentally, I discovered that cards representing data from tumors of the same type often looked alike in that they bore holes in similar locations. It seemed that automated pattern recognition of such data should be possible, given the right decision model. At about this time Lee Lusted, who I had come to know through mutual friends, showed me an article which he and Ledley had published in Science (8). This very timely paper dealt with the logical basis of medical decision making, and obviously was of great importance to me. However, at just that time I was appointed acting dean of the medical school at Columbia, where, as in most new schools, a crisis atmosphere prevailed. By the time that things had settled down, Homer Warner had successfully applied Bayesian logic to the diagnosis of congenital heart disease (9).

None the less, all of the parts of a computer diagnostic model for bone tumors were there awaiting application. Lee Lusted had become the Chairman of the newly formed NIH Committee on Computers, and was looking for suitable research to review. I submitted an application entitled "Computer Analysis of Tumor Roentgenograms", and later was delighted to receive notice from the National Cancer Institute of a research award, effective January 1962. This research award was a key event in that it strengthened my interests in research and clinical radiology, and diminished my interest in the Dean's Office. It also permitted me for the first time to recruit substantial

programming assistance. I had the the good fortune at that time, and later, to have the enthusiastic support of research colleagues of great competence, whose creativity, drive and dedication more than matched my own.

The first product of this research grant was in the domain of computer aided diagnosis (CAD), a diagnostic system where a human scans the image, identifies the sign information and enters it into the computer. By contrast, automated image diagnosis is a system where the image is scanned under computer control and the sign information is identified through the use of algorithms specific to each problem. In either system the predictive data from a case are the input into a program which uses decision rules functionally equivalent to those used by an expert. After analyzing the data, the program produces output in a format convenient to the user. The data input may be signs, symptoms, laboratory results, or whatever the diagnosis requires. Developing such a program may involve a dialogue between the expert and the programmer in order to code the rules which the expert is using in the flow of the logic. To gain more experience, additional cases are run and solutions to wrong responses are agreed upon. The iterative process is continued until the results are optimized. This basic process can be improved by substituting a generalized program with the rules not being a part of the program itself, but rather as a separate source of input. This means that the expert can modify the program by simply plugging in a new set of rules.

BAYES THEOREM AS A DECISION RULE (10)
We found that we had the choice of using one of two methods of implementing Bayes' theorem which had been evolved for purposes of diagnosis. The first, which deals with symptom patterns, was described by Maxwell (11) and by Ledley (12). It has the advantage of taking into account the interrelationships of the predictor variables. They need not be independent. It has the considerable disadvantage that, if the number of variables is large, an unwieldy number of possible symptom patterns must be considered. The second approach, which we used, is due to Warner and his associates (9). It is a much simpler method to implement, but requires that the predictor variables must be independent. I have had good results with the latter method even though not all variables meet the prescribed requirement of independence.

In order to implement this latter approach, a prior probability matrix was assembled, which consisted of the relative frequency of each binary variable, compiled separately for each disease. Preparation of a probability matrix is a major task, and heavily dependent upon the

integrity of signs. Also, it is dependent upon several other factors, including the adequacy of the population on which it is based, and the accuracy of the pathologist's classification, on the basis of which each case is assigned to a disease class. However, such empirically derived prior probability matrices need not be considered as sacrosanct. Maxwell (11) sets forth a method whereby, in the light of statistical decision theory, equal prior probabilities may be assumed and then be suitably adjusted on the basis of the errors of misclassification to which their use led. By whatever method they are derived, the prior probabilities are at the heart of the Bayesian diagnostic process.

THE IDENTITY AND MEANING OF SIGNS

The quality of the sign input into this system is extremely important. When I was first identifying the signs to create the bone model, I had my own idiosyncratic meanings for the sign information that I used. This collection of signs was my personal model. However, there is a broader concept which must be observed for a radiologic sign to be effectively used. Each sign should be a reflection of a unique morphologic event. Once the sign is recognized, this uniqueness must be described, illustrated, and correlated with the anatomic changes which the sign reflects, so that when your colleagues recognise the sign, they receive a useful message, such as "I represent calcified neoplastic cartilage." At this point the sign has earned inclusion in what is known as the public model.

The other important attribute of a sign is its conditional probability. For example, take the relationship of permeated bone destruction, an easily recognizable sign which implies a rapid rate of growth, to each of four common tumors of bone. This sign may be found in 95% of Ewing's sarcomas, 20% of chondrosarcomas, 5% of eosinophilic granulomas and zero percent of osteoid osteomas. Given an unknown tumor of one of these four classes, it is clear that the most probable diagnosis, based on this sign alone, would be Ewing's sarcoma. The possibility of osteoid osteoma would be totally excluded. Most skeletal radiologists have an intuitive understanding of conditional probability, and based upon their personal experience, can assemble a quite creditable probability matrix for the signs related to musculoskeletal diseases.

OUR FIRST PAPER on CAD of bone tumors was presented at the meeting of the Radiological Society of North America in the fall of 1962 (13). Seventy-seven cases with eight different diagnoses were diagnosed with 77.9% accuracy. Other papers followed in succession (14,15,16,17,18). For the fall 1964 meeting of the same

society, Lee Lusted and I teamed up to take a small IBM computer, key punch, and printer onto the scientific exhibition floor of the Palmer House in Chicago. There we variously amused and astonished our audience by performing on-line diagnoses "on the spot," receiving the magna cum laude award. In 1965, we took the same show to the International Congress of Radiology in Rome.

IMPROVING THE PERFORMANCE OF CAD PROGRAMS

For human interaction with the computer, the response time must be fast, and the questions limited to a number which is acceptable by the user. No one likes to use a CAD program which repeatedly asks for the same information as if it had no memory. For these reasons, we have found automatic answer vectors to be necessary for eliminating the possibility of asking questions which are illogical in a given situation, or which have been previously answered in another way. In this manner, the computer interaction of the human scanning the image can be made clean, neat and brief.

We have found decision trees to be very useful in developing the logic of a diagnostic situation. We designed an extensive set of decision trees for the purpose of reducing the number of possible diagnoses prior to carrying out Bayesian analysis. Surprisingly, we have found that humans make errors in following even the most simplistic decision trees. Further, we found that an error involving taking the wrong branch on a decision tree resulted in the wrong diagnosis 48% of the time. This has cooled our enthusiasm for decision trees, since an alternative logic is available for use.

Further, we have found through testing that humans make many errors in identifying signs. For establishing an experimental data base which reflects the gold standard of signs, the truth of each sign can be established by double reading, with a third reader to break ties. Signs so confirmed are called "book signs". In a recent study of a test set of 245 cases of histologically proven bone tumors, where we used 40 signs to differentiate between 30 diagnostic possibilities, a first choice accuracy of 79.6% was obtained with CAD and book signs. An accuracy of 93.1% was achieved where the criterion is that the correct diagnosis is one of the three highest probabilities listed by the computer. This is to be compared with an average sight reading accuracy of 55.4% for four experimental readers, and when the readers selected the signs, 59.3% for CAD. These significant differences show that inaccuracy of human interpretation of signs is a major cause of diagnostic error in CAD. For this reason, it is of critical importance that signs be meticulously

defined and illustrated, and that critical decision points are not based upon differentiating two signs which are so similar that they are likely to be confused with each other.

COMMENT: Despite these problems in human performance of sign identification, it has long been my experience that CAD effectively illustrates the sensitive relationships between signs and diagnosis, and that CAD is an enormously effective teacher of the meaning of signs and of how the diagnostic process works. Recently, I have found CAD valuable for recording and evaluating radiologist performance, in sign recognition.

RADIOLOGICAL ASSESSMENT OF GROWTH RATE

Most experienced radiologists develop an intuitive feeling as to whether the radiologic image is that of a benign or a malignant bone tumor. In testing the signs and measurements which comprise the radiologic model of bone tumors, it is clear that most such variables are related more to the aggressiveness of tumor growth than to histologic type. Indeed, diagnosis of tumors from radiographic information is so difficult because it is a diagnosis of inference and based upon secondary evidence of histologic type. That is, Ewing's sarcoma is inferred to be Ewing's sarcoma because of the tumor's typical location and size, its permeated pattern of bone destruction, and its absence of tumor bone formation; not because the radiologist is permitted to see and recognize the particular cells of Ewing's sarcoma. The pathologist, on the other hand, does see the abnormal, highly cellular structure characteristic of Ewing's sarcoma, but little of the evidence of growth rate which characterize the radiographic image. The two kinds of evidence, radiologic and histologic, complement each other extraordinarily well, yet neither may be regarded as a total substitute for the other.

In recognition of this direct relationship between the radiographic image and the growth rate of a focal lesion of bone, I constructed an algorithm to grade aggressiveness into one of five different rates: IA, slow or static; IB, moderately slow; IC, intermediate; II, moderately fast; and III, fast (19,20,21). The algorithm for determining rate of growth is effective for grading particularly those lesions where destruction of bone is present, and is deceptively simple, requiring binary decisions on only six signs in combinations of three or less for each grade. The logic of the grading sequence is based upon the known predictive values of each sign, and is such that failure to recognize a sign biases grade selection in favor of a more rapid estimate of growth. The performance

of the algorithm has been extensively tested with the computer, its results statistically proved, and its design simplified in order to improve human performance in grade selection. The ultimate value of the radiologic grading system lies in its ease of human application and in its usefulness in evaluating the behavior of bone lesions in the clinical setting.

CRITIQUE In perspective, two systems for diagnosing bone disease have evolved out of a study of the identity and meaning of radiological signs: one is a logical, computer based, probabilistic methodology for diagnosing bone tumors; the other a computer designed but human mediated methodology for estimating rate of growth. The CAD system requires human interface with a computer, enough time to select and record the signs that are observed, and ultimately produces a product in minutes which the user of the system is trained to produce in seconds, with his own logic, and his own "built in computer". If the user of CAD can operate the system successfully, it is because he already has memorized the signs that are necessary for diagnostic decision making, and quite possibly he regards thinking on his feet as more effective, and more fun than thinking with a computer.

On the other hand, the algorithm for assessing rate of growth provides a kind of information that is not otherwise available to the user. If a physician wishes to use an x-ray to assess rate of growth, the logic for the computer and for the physician is exactly the same, and the results will be exactly the same. There is no alternative logic to be used in accomplishing this objective. The computer does not do it better, or faster, than the human. And because of its ease of application and its simple values, the use of radiologic grading of rate is a world-wide phenomenon.

AUTOMATED IMAGE ANALYSIS

During the early sixties, research in computer aided diagnosis and the development and testing of The Missouri Automated Radiology System kept our program at Missouri exceedingly busy. During 1967-68 I spent a sabbatical year at the Middlesex and the Royal National Orthopedic Hospitals in London, working on an atlas of tumors of bones and joints, and learning more about orthopedic radiology. I had left the clinical department under the able leadership of Arch W. Templeton, and computer research in the hands of Professor Peter Reichertz. I returned to find that the research program was progressing admirably, but that Arch Templeton's departure to the chairmanship of radiology at the University of Kansas had created a clinical void which could be filled only by me. Nevertheless, seeds

planted in bioengineering before my departure had borne fruit, and I found that Samuel Dwyer and his colleagues had been working toward digitizing radiological images through the acquisition of suitable computing and image scanning equipment. In view of my administrative responsibility to the clinical department, my commitment to completing a book, and to direct substantial research and research training programs already funded, further involvement in a major research program was a very risky business. Yet, the forward momentum was already there, and a great research opportunity would dissipate for lack of radiological leadership unless I stepped forward. At that time, no task seemed beyond accomplishment to me, so I joined with Dwyer in raising the funding for a program project entitled "Diagnostic Content and Redundancy in Radiant Images". A team headed by James Lehr had already made substantial progress in developing algorithms for the detection of abnormalities in brain scintigrams (22). These results plus an impressive array of state-of-the-art technology convinced the site visiting team that we knew what we were doing and as of September 1970 a program project research award was granted for support of automated image analysis. These were heady days, and in retrospect, we really did know what we were doing, but were doing it probably some ten to twenty years ahead of clinical application.

Our first major success was in the direct computer diagnosis of rheumatic heart disease, accepted for publication in September of 1971 (23). This project led by David L. Hall, a research trainee in radiology at Missouri, described the technical details of programs which identified the cardiac silhouette, measured its important parameters, and applied discriminant function analysis to decide whether the heart shadow was within limits of normal, and if not, which kind of rheumatic heart disease best fit the findings on the film. The computer had substantially greater success in classifying rheumatic heart disease than the radiologists had in viewing the same library of proved cases.

These accomplishments, along with technical proceedings dealing with the automated recognition of bone disease, were not unnoticed either by radiologists or the press. We had chosen to work in the domain of both chest and bone for the same reasons that I had chosen to model images of both chest and bone; the contrast and spatial resolution inherent in the images of these regions are such that edges, shapes and textures could be identified much more easily than in images of other anatomic regions. However, although I was a recognized expert in bone disease, I was treading on the turf of those who were more expert in the fields of vascular and pulmonary diseases, which was a sin that

was difficult to forgive. The press responded by writing us up in the news magazines, while my vascular and chest radiological colleagues responded by attempting to shoot us down in the grants review process. Sam and I did our best to show that we were attempting to implement technology rather than to invade new turf, but the nature of our success in automating the process of clinical decision making was too threatening to be tolerated. So in the mid-seventies, at the time when we began to face stiff competition from computed tomography for the available research funds, we experienced an unsympathetic site visit and lost our support.

I turn now to two projects in the domain of automated diagnosis, which illustrate some important relationships between humans and computers.

AUTOMATED DIAGNOSIS OF CONGENITAL HEART DISEASE

This first project deals with the evolution of the man-machine interface necessary to optimize success in computer recognition of six classes of disease in congenital heart disease. To establish a base line of human diagnostic performance, three radiologists interpreted a data set of 387 cases, with an average human accuracy of 41%. The first task was to determine if the computer could do as well as the radiologists. Beyond carrying out the necessary preprocessing operations, just getting the computer to identify the heart seemed a monumental step. The task was made especially difficult because the films to be analyzed ranged in size from infants to adults. Next, the primitive tasks were to find edges, trace contours, and to merge regions. A problem easy for humans but difficult for the computer was to find the left leaf of the diaphragm when there was a large bubble of air in the stomach under the diaphragm. Here the edge finding algorithm followed the edge of the heart through the diaphragm into the stomach bubble, until a special "fix" was prepared.

The diagnostic predictors consisted largely of measurements and Fourier pairs which contained information about edge shape. Given the outlines that the computer traced, computer accuracy was 40%, using the same films that the radiologists had examined (24). To determine if hand tracing of edge information would yield more accurate results than if the computer found the edges on the films, we had the computer examine clear plastic overlays on which edges had been traced (25). Diagnostic accuracy was improved by 25%. At this point further improvement was minimal until the radiologists called attention to the use of individual segments of the cardiac silhouette for clinical diagnosis, instead of the entire silhouette. A new

computer model, which used Walsh descriptors for each of five cardiac segments, and with inflection points marked on the film by the radiologist, yielded an overall accuracy of 70%, nearly 75% better than the radiologists had achieved (26).

CRITIQUE Before we fully understood how human intervention would be needed to resolve the complexity of this problem in image analysis, the radiologist often felt a little like a spectator on the sideline, feeling outmoded by the machine and the engineers. An important lesson learned from this study is that humans and computers each have their special areas of competency, and that the goals of automated image analysis can be more rapidly furthered by a carefully designed symbiotic effort. To the radiologists, an attractive feature of this study is that results are not produced by computer magic;--humans can understand the process that the computer is using to achieve results, and through experience modify the process to provide better results.

AUTOMATED ANALYSIS OF TEXTURE IN BONE

We now turn to the second project which deals with discrimination of textures, a topic vital to radiology. We are all aware of the adjectives spotted, honeycombed, fluffy, etc., in the radiologist's descriptive vocabulary. It is in the development of computer programs that differentiate between textures that the radiologist really finds himself in the role of a spectator on the sideline, as will become apparent later. However, as an orthopedic radiologist I had become expert in distinguishing between the textures of Paget's disease and diffuse neoplastic infiltration in spongy bone, and was able to spell out the basic parameters of an interesting problem for texture identification. There are four such parameters, but the most important is the texture of spongy bone itself. A data base of 163 cases was used for this study. Areas of interest, excluding cortex, that were selected by a radiologist were viewed or scanned through windows cut in opaque film. The radiologists participating in the experiment were asked to examine each case, and to make a decision whether the trabecular structure reflected normal bone, Paget's, or carcinoma.

It is possible for the texture identification algorithm used here to differentiate mathematically different texture patterns which cannot be discriminated by a human observer. Computationally the heart of this spatial gray level dependence method is a so-called spatial gray level dependence matrix which is computed from the digital image along the directions 0 degrees, 45 degrees, 90 degrees, and 135 degrees from center, from each of which the 2nd order probabilities

probability of correct (2) minimax probability of features of energy, entropy, correlation, local homogeneity and inertia are derived. Five features extracted for each of four orientations give 20 measurements of texture, or even more if more than one intersampling distance is considered. Measurement selection techniques consisted of a forward sequential search algorithm judging each group of measurements by one of the following: (1) maximum overall probability of error, and (3) maximum 10% jack-knife overall correct. The testing results for this study show overall accuracy roughly equivalent to human performance, but better than humans for identifying normal trabecular bone (27).

CRITIQUE These are regarded as excellent results which probably could have been improved by increasing the size of the data set. From the engineers perspective there are problems with this methodology in that the engineers are unfamiliar with the clinical environment and with textures of bone, and the radiologists have little theory to offer them to guide the development of texture discrimination. The radiologists, on the other hand can see the excellent experimental results, but cannot causally relate these results to their own experience in recognizing textures. It would be helpful if the computer scientists were able to reconstruct the physical features of textures from the mathematically defined information derived from the test data, in order for the radiologist to be able to recognize such features, and to improve his own skills in texture identification.

WHAT OF THE FUTURE?

I have unqualified enthusiasm for the future usefulness of automated image analysis, but reserved enthusiasm for computer aided diagnosis. The reasons are as follows:

(1) The trend in diagnostic radiology is toward an increasing use of digital imaging. We are now beginning the use of prototype systems which provide chest and bone images in digital format *de novo*, with the implication that the pre-processing that formerly was necessary can largely be eliminated. Image information will be directly available for analysis.

(2) Radiologists have learned to deal with digital images and displays on a daily basis. In my opinion they will welcome computer tools which can provide information which they need and cannot obtain in any other manner.

(3) With the advent of digital image management systems, images will be accessible on displays at the radiologist's work station. Image processing tools will become available first hand.

Given the need for man-machine interface in solving some problems in pattern recognition, the radiologist's work station may become a natural setting for such an interface.

(4) There is a need for sophisticated programs to differentiate and qualitate textures. We know that some such programs can differentiate textures which look alike to humans. In my practice as a skeletal radiologist, I would like to have such programs now; I would use them to distinguish between Paget's disease, fibrous dysplasia, and chronic infection. I believe that chest radiologists need tools to differentiate textures in lung disease.

(5) The need for programs to measure and calculate is limited only by the imagination.

(6) CAD of images requires reliable data input; humans are inconsistent in identifying signs. Data entry can be tedious and time consuming. With the availability of the radiologist's work station, the easy access to special programs may in time make CAD more acceptable.

(7) The usefulness of CAD as a teaching aid has not been fully appreciated, and needs to be further evaluated.

(8) The role of artificial intelligence in enhancing decision making from images has not been sufficiently explored.

CREDITS

Through the years following the original award of support for computer analysis of tumor roentgenograms, major collaborative contributions were made by, among others, Cosmo Haun, Theodore E. Keats, Lee B. Lusted, James L. Lehr, Arch W. Templeton, Arch H. Turner, Jr., Peter L. Reichertz, Robert P. Covert, Jay Goldman, Samuel J. Dwyer, Robert W. Parkey, Charles A. Harlow, Timothy A. Salthouse, John J. Sterling, Roger A. Bauman and Jaime Taaffe. These scientists participated in federally and otherwise funded research projects on computer aided diagnosis, simulation of patient and information flow in radiology departments, radiology information systems, automated image analysis, human processing of radiological information, research training in radiology, and clinical cancer training. The contributions of Peter Reichertz, James Lehr and Sam Dwyer were of special importance because of their close relationship to me over a period of many years; theirs and the contributions of all others are gratefully acknowledged.

Gwilym S. Lodwick, M.D.

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Recollections on the Processing of Biomedical Signals

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Summary

The processing of biomedical signals took many steps forward in the two decades that followed the introduction of digital computers to the field in the late 50s. Along with my colleagues at the Central Institute for the Deaf and at the Biomedical Computer Laboratory, I was privileged to participate in this exciting early period of biomedical computing. Some of my experiences with projects, both successful and unsuccessful, in evoked response audiometry, neurophysiology, fetal electrocardiography, radiation treatment planning, electrocardiographic rhythm analysis and ambulatory monitoring of electrocardiographic rhythms are described. These recollections give less attention to scientific results than they do to selected anecdotes and observations.

Introduction

These recollections stretch over seventeen years of biomedical computing at the Washington University Medical Center, starting in 1958 at the Central Institute for the Deaf (CID), through the period 1964 to 1975 at the Biomedical Computer Laboratory (BCL). The period from 1975 on will not be covered for reasons I will try to explain. Since 1975 I have been at the Department of Computer Science, as Chairman, and some projects started then are still underway. Since

I want to try to report both successes and failures, and since achieving any degree of objectivity in these matters is difficult, no attempt will be made to report on recent events. In addition, these historical recollections provide an opportunity to report sidelights and difficulties that ordinarily do not find their way into the pages of the regular journals. I hope these touches of reality are useful to those whose picture of biomedical computing is drawn primarily from their reading of the scientific literature. With the perspective of the years such moments have softened and I hope you will find them either interesting or amusing.

In keeping with my half of the theme of this session these recollections are limited to signal processing, although I will take the liberty of finding an excuse to discuss one other project that provides some interesting sidelights.

Auditory Evoked Responses

My interest in biomedical computing had its beginning when Hallowell Davis, then Director of Research at CID, asked me to investigate methods for the measurement of the auditory evoked response in infants. The goal was to determine whether, despite their inability to communicate, these young children had hearing deficits. The experimental technique was that of Dawson [1] and required the averaging of scalp potentials synchronized to a repetitive auditory stimulus.

My background was electrical engineering and acoustics. In 1958 I was just beginning to learn about transistors and was completely unfamiliar with digital computers. Some study convinced me that the use of a special-purpose digital computer was the method of choice for the evoked response problem. Since a description of the first digital Average Response Computer (ARC) [2] was yet to

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be published and nothing was available commercially, I enlisted the help of three graduate students at CID, first Don Glaeser in 1958, Kirti Charan in 1959 and Maynard Engbretson in 1960. They tried three different approaches to the problem. One was a difficult design with excellent operational speed and low cost. The second seemed to be a quick and inexpensive design with tediously slow operational speed. The third required a substantial design effort and was not cheap, but did promise good operational speed.

It was neither the first nor the last time that I learned the hard way that the three competing objectives of rapid realization, low cost and high speed cannot be achieved in a single design. If you are experienced in the area, you can get two out of the three. If you are inexperienced, as we were, you had better try for just one of the three objectives. The approach tried by Glaeser and me turned out to be extremely difficult, attempting as it did to achieve two of the three objectives. It was eventually abandoned, but more of that below. The approach I recommended to Charan, also an attempt to get two out of three, met a similar fate. Engbretson's approach attempted only one of the three objectives, high-speed, and a prototype was operational by late 1961 [3], [4]. A later version [5] incorporated the lessons learned from the prototype and by 1963 was in regular experimental use in Davis's new auditory evoked response laboratory where it met all the technical goals set for it.

Taking only slightly less time than the design itself was the selection of a suitable acronym for Engbretson's special purpose computer. We settled on HAVOC for Histogram, AVerage and Ogive Calculator. Once having gotten the hang of finite state machine design, we decided to incorporate the tabulation of frequency distributions (*histograms*) and integrals of frequency distributions (*ogives*) although little use was to be made of these two modes of operation throughout the years. Davis used HAVOC's *average* mode to create the field of auditory evoked response audiometry, now a standard technique in the evaluation of infants with possible auditory deficits [6], [7]. HAVOC was last used in 1982 after almost 20 years of productive service [8].

Neurophysiological Signals

Hallowell Davis's auditory physiology lab-

oratory at CID contained a Grass camera and a variety of amplifiers for the low voltage electrical signals that he and Donald Eldredge recorded from guinea pigs and chinchillas. The camera was used to record photographically multiple simultaneous waveforms obtained from microelectrodes inserted in the experimental animal's inner ear.

The first design mentioned above was to not only process auditory evoked responses, but also serve as a data acquisition system for the neurophysiology laboratory. To meet these objectives Glaeser and I attempted to build a high-speed average response computer based upon a magnetic drum memory. The goal was to obtain increased storage at lower cost than was possible with the ferrite core memories of the day. It was a very educational experience for me, but the system never arrived in the laboratory. Timing constraints imposed by the rotating drum and high sampling rates required by the neurophysiological signals combined to increase the complexity of the design beyond what I could manage. We learned how to design a high-performance analog-to-digital converter [9], we learned about fast digital circuitry and I learned that Nature abhors a magnetic drum. Finally, I learned the importance of upbeat acronyms. DARC, standing for Drum Average Response Computer, never had the appeal of the more neutral ARC or even the somewhat chaotic sounding HAVOC.

The LINC

Now that is an example of a high class acronym, the Laboratory INstrument Computer. It was to change my life and to change biomedical computing. My part of this story begins during the design and construction of DARC. I had become aware of a new digital module manufacturer in Maynard, Massachusetts, and decided to visit the plant to see if their products lived up to the attractive literature circulated by this "new start", Digital Equipment Corporation. Ken Olson was available to this visitor from St. Louis, who just happened in off the street that spring morning in 1962, and we talked about DARC and a new stored program computer that I had in mind for the CID neurophysiology laboratory. He suggested that I drive over to Lincoln Laboratory to visit Wes Clark who was working on a similar project called the LINC [10].

I did just that and found that the Lincoln Laboratory group was well ahead of my thoughts on laboratory computers. Not only had Clark designed a computer that for its day was ideally suited to the neurophysiology laboratory, but his group had a prototype running and I was able to try some simple graphic routines. The console was a delight to use and the logic and timing drawings were elegant and easy to understand (apparently a lost art). It was a tremendously exciting afternoon. More or less on the spot, I decided to abandon my efforts to design a stored program computer for CID and instead to join forces with the Lincoln Laboratory group. They were to move shortly thereafter to MIT, at Kendall Square, to carry out the LINC Evaluation Program, an NIH/NASA sponsored program for the construction of a dozen machines for biomedical scientists at as many institutions throughout the nation [11].

By the fall of 1963 we had a running LINC at CID assembled from one of ten or so sets of parts acquired for a series of phantom machines purchased in parallel with the twelve legitimate machines for the LINC Evaluation Program. Norm Kinch, drawing on his Navy Chief experience, had arranged for the phantom machines through creative purchasing, all for the benefit of the other organizations outside the Evaluation Program who, like CID, saw the advantages of the LINC and wanted to participate in the revolution in laboratory computing it represented.

The LINC was installed in the CID Physiology Laboratory, now under Eldredge's supervision as Davis was spending most of his time with HAVOC in his new auditory evoked response laboratory. Eldredge and a succession of collaborators used the LINC in their work until 1980 when it was finally retired after seventeen years of nearly trouble free service.

The Beginning of BCL

In 1962 I was asked to serve on the NIH Computer Study Section with Lee Lusted as chairman and Bruce Waxman as executive secretary. One day after the study section business was done, Lee asked me whether I might have an interest in starting a research resource in biomedical computing at Washington University. The Research Resource Program was a new initiative of the Institute for General Medical

Sciences of NIH. The atmosphere was expansive and optimistic, a contrast to the character of the NIH grant process today. Soon the program was taken over by the newly formed Division of Research Resources operating out of rented quarters in North Bethesda. Dazzled by these developments I prepared, with considerable enthusiasm, a grant application for a new Biomedical Computer Laboratory at the Washington University School of Medicine.

During the period 1958 to 1963, I had assembled a group of graduate students at CID interested in biomedical computing that included Don Glaeser, Maynard Engebretson and Floyd Nolle. When the BCL grant was funded there was no home for a new computer laboratory at the School of Medicine. We looked around the Medical Center and found nothing but an old garage building about four blocks away from where we expected to find our collaborators. With heavy heart we took steps to complete arrangements to renovate the garage so that it could accommodate our new laboratory, but at the last possible moment an excellent location, the old Shriners Hospital, was acquired by the Medical Center. Renovations were still in order since the buildings were about 40 years old and in poor repair. While remodeling proceeded, CID generously allowed us to continue to work in their research space. During this period our small group was joined by several full-time staff members including Sharon Davisson, Mike McDonald, Bob Kimack and Fred Francis. Finally, on April 15, 1964, eight of us moved into freshly painted laboratory space at the old Shriner's Hospital nurses quarters, 700 S. Euclid Ave., where BCL continues to operate today.

Less than three months after BCL opened, Bill Papien, Wes Clark and members of the LINC design team moved to Washington University from MIT. Norm Kinch joined the group after a year spent in the southwest and Charles Molnar, co-designer of the LINC, moved to St. Louis from Boston two years later. A sister organization to BCL was formed which is now known as the Computer Systems Laboratory. Thus began a long and fruitful collaboration between the two laboratories.

Fetal Electrocardiography

One of the first projects to be initiated at BCL was a collaboration between Remsen Behrer,

a pediatric cardiologist, and Don Glaeser in which signal processing techniques were used to recover the fetal electrocardiogram (ECG) from electrodes on the mother's abdomen. Normally the maternal ECG is many times larger than the fetal ECG, making it difficult to recognize abnormalities in the fetal heart beat. The LINC was used to obtain a representative maternal ECG waveform by calculating a running average synchronized with a signal obtained from shoulder leads. This representative maternal ECG waveform was then subtracted from the total abdominal signal leaving the fetal ECG waveform.

Was the project successful? From an engineering point of view it was, but from a clinical point of view, it was clumsy, ahead of its time and not useful during labor. Positive scientific results were reported [12], but the technique did not find popular clinical support. With the fetal ECG team in attendance the LINC produced results rapidly, but the patient had to be brought to a special laboratory at a scheduled time. It was not clear then that the value of the test was great enough to overcome this inconvenience. Both Behrer and Glaeser left Washington University to follow other career opportunities.

Ivan Sutherland years ago described the wheel of reincarnation in display technology. Perhaps he will pardon my application of his phrase to a different situation: Good ideas get reinvented periodically until some combination of circumstances (convenience, cost, need) causes the invention to become widely accepted. The idea presented in 1968 by Behrer, et al, had important and novel features, but recording the fetal ECG was not new (13). It was the best version of the technique up to that time, since it required no vaginal electrode, but even today the idea continues to be reintroduced. Do we want to increase our vigilance to prevent journals from publishing another turn of the wheel of reincarnation? I think not. Circumstances change and an old idea may become practical in a new environment or with a new twist.

The Programmed Console

The Programmed Console (PC) grew out of a computer design class that Wes Clark and I taught in the spring of 1965. The design was less powerful, but in many other ways much like that of the LINC. An important distinction was that

the PC incorporated as a standard feature a modem for data communication with a host computer and thus became an early workstation (although we did not know the term in those days) sharing the computational load with the host.

After the class had finished, I redesigned the PC with help from Bill Gerth for a major DRR supported project in radiation treatment planning. The idea for the project occurred during a meeting with Bruce Waxman held in the summer of 1965. Bruce was then head of the Biotechnology Resources Program at DRR and I showed him some photographs of radiation isodose contours Bill Gerth had produced to show off the PC's graphic ability. He became interested and we planned an evaluation program that would place the PC in a few leading institutions. Competitive bidding lead to a contract with Spear, Inc., Waltham, Massachusetts, for the construction of six PCs, one for radiation therapy at Washington University, four for other therapy units in the U.S. and one for the Ontario Cancer Institute.

This radiation treatment planning project had nothing to do with signal processing, but is introduced here because it bears on the next topic, and also because it gives me an opportunity to relate several stories that may provide interesting historical sidelights. The origin of the name PC is one such sidelight. During the last frantic weeks of the spring '65 class we had dubbed the two machines being designed and built by the class "The Four Week Wonders" or, following the lead of a then popular television program, the 4W2¹. When it was clear that the 4W2 was going beyond the end of the spring 1965 semester, Bob Ellis, a participant in the class, suggested that we needed a more dignified name. He proposed "Programmed Console" since the machine we had designed was like a computer console (or terminal), but yet it was programmed. Little did we know that sixteen years later the two letters "PC" would be appropriated to play a fateful role in a new era in computing.

The second story concerns an unexpected development on the machine delivered to Jack Cunningham at the Ontario Cancer Institute.

¹For the youngsters among us, a popular 1965 comedy news show was titled, "That Was The Week That Was" or TW3.

One of Jack's research assistants, Joe Milan, wrote a space war program for the PC over a couple of weekends shortly after the machine was delivered to Toronto in 1967. Joe called the program Hyperspace because in this version of the famous computer game missiles and spacecraft could fly out one side of the display and immediately reappear flying into the display on the opposite side. Hyperspace was provided to all six PC sites and somehow appeared on all the development machines at BCL. Because the CRT display was an integral part of the PC, the responsiveness of the space war game was excellent and it became an instant hit within the PC community.

The first indication to me of how pervasive Hyperspace had become was a plague that was visited on a pair of keys on the PC keyboard. It turned out that the keys were failing so often because they were used as the two missile firing keys in Hyperspace. Bill Gerth and I realized that we were witnessing an important phenomenon, but we had done an inadequate job in our market analysis. We considered putting PCs into airports, but figured we would have to charge at least 50 cents a play and, after all, who would be foolish enough to continue to pump quarters into a computer game?

The final story concerning the PC had its denouement just this year. In addition to the superb stand-alone external beam treatment planning programs developed by Bill Holmes, the modem on the PC allowed us to send data to the host computer for the calculation of the dosage pattern from interstitial radioactive implants. Through communication programs developed by Liz Van Patten and Dave Bridger, the PC functioned as a data entry device instead of the keypunch that had been used previously. It was no longer necessary to transport cards to the central computing facility and, furthermore, results could be returned promptly via the same modem connection to be displayed or plotted by the PC. All of this was operating by February of 1967, reported in the literature [14] and preserved on motion picture film.

In 1973 a patent was granted to a firm that is now defunct claiming as an invention a similar system for data entry. In the mid-sixties none of us gave a second thought to patenting the PC because we felt the technology was obvious in the light of the development of the LINC. Over the

last decade the present owner of the 1973 patent has sued several manufacturers of smart terminals for an aggregate well into nine figures. Wes Clark and I recently appeared as witnesses for the defense in the latest of these cases. We supported the position that the PC and the LINC anticipated the patent and compromised the validity of the 1969 filing and the subsequent 1973 patent. The judge will soon decide whether that position is correct, but however he rules there is a significant point for biomedical computing: biomedically inspired research and development can lead the way for technology in general. Clearly the LINC was such a pioneering development and so too, in its own area, was the PC.

Electrocardiographic Rhythm Analysis

One of the advantages of a major project like the development of a computer system for radiation treatment is that the design group is likely to have a few extra machines around before it's all over. Our prototype PCs were not as fast as the Spear PCs and were much less attractive. We felt they were inappropriate for our radiology collaborators at other institutions and thus were ripe for application to another project at BCL. Such a project was the automatic detection of cardiac arrhythmias which had begun in 1965 on the LINC, but by the fall of 1966 had been transferred to two prototype PCs that were subsequently dedicated to the project.

In fact, our original objective had been to develop a system for the diagnosis of 12-lead ECGs, but in 1965 that seemed excessively difficult for a first venture into pattern recognition. Harry Fozzard, who was our initial cardiological collaborator, Floyd Nolle and I thought we would first spend a year or two warming up our skills on a much simpler problem: the detection of cardiac arrhythmias from a single chest lead. Actually BCL has spent more than twenty years on the arrhythmia problem and we never did get around to the diagnostic ECG problem. So much for planning in research.

The first step in our rhythm analysis project was Floyd Nolle's invention of a preprocessing routine that reduced the input data rate to the analysis programs, but retained enough information for them to carry out an accurate rhythm diagnosis. The program transformed the sampled ECG data to a series of horizontal and

sloping line segments. I think it was Charles Oliver, a second cardiological collaborator who joined the project in 1966, who looked at the preprocessor output and commented that it looked like a profile view of an Aztec temple. It did, and so we began an intense effort to find a good acronym expansion. After rejecting many names as unimaginative or baroque, I began an exhaustive search of appropriate sections of the unabridged dictionary and ultimately decided on "Amplitude-Zone, Time-Epoch Coding", a name which fit the algorithm tolerably well.

Aztec worked well on ECG data, producing a compression of about 10:1 with enhancement of the waveform components needed for later analysis. We were eager to publish our result and thought a letter in *Science* would reach the right group of readers. It was, alas, rejected because it was "of interest to only a limited audience." Later published in the *IEEE Transactions on Biomedical Engineering* [15], it has been cited widely for over a decade and more recently appears without citation having become a part of the language of rhythm analysis.

In the fall of 1969 the Barnes Hospital Coronary Care Unit (CCU) opened under the direction of Gerald Wolff. Floyd Nolle, Charles Oliver and I had worked hard during the previous two years to develop an ECG monitoring system called Argus² (ARrhythmia GUard System) that could be used 24 hours a day to alert CCU staff to life-threatening arrhythmias [16], [17]. The early experience with Argus was exciting and rewarding as a result of the exceptional support we received from Gerry Wolff and several members of his new nursing staff.

An example of the excitement occurred not long after the unit had opened. A patient that the monitoring equipment indicated to be in ventricular fibrillation was observed by the responding "code" team to be sitting up in bed eating lunch with no signs of a life-threatening arrhythmia. How could this be?

The mystery was solved by Floyd and Dieter

²According to Webster's Third New International Dictionary, Argus was a "mythological being with many eyes some of which were always open, known as a zealous watchman." The choice of this acronym was due to Charles Oliver.

Ambos who discovered that a nurse walking on the CCU's special antistatic carpet caused the thin conducting wires embedded in the weave to modulate the signal from a nearby TV station. This fluctuating signal carried by the carpet's conducting wires was rebroadcast particularly strongly inside one patient's room; was picked up by the monitoring leads there; was accidentally demodulated by special loose-lead circuitry, the latest "improvement" in the ECG monitoring amplifiers; and simulated with surprising faithfulness ventricular fibrillation on the monitor's screen and in the monitor's circuitry itself.

The ability of the "code" team to detect absurdity is, thankfully, much better than it can be in any computer and no harm was done by this highly improbable combination of circumstances. The episode does emphasize the inability of even the most careful designers to think of all possible contingencies. Staff who distrust equipment and think for themselves are essential to avoid serious consequences during the initial period of use of automated equipment in a clinical environment. Only after considerable experience and a careful cataloging of the modes of equipment malfunction should the staff become comfortable enough to suspend their adversarial relationship with the equipment.

A clinical evaluation of the operational impact of Argus was carried out in the CCU in 1971 and 1972 by a team led by Charles Oliver. The results [18] showed that for one group of CCU patients Argus produced more than twice as many treatment actions as observed in an equivalent control group. The only difference between the two groups was that the output of Argus was available to the CCU staff in the study group, but withheld in the control group.

If treatment actions, such as the administration of lidocaine, can be beneficial to the patient, should we deduce from these results that computer monitoring is beneficial? Each therapeutic treatment has its associated medical risks and benefits which our clinical study made no attempt to address. These are medical questions that require a clinical study well beyond the scope of ours, dealing as it did with only the operational impact of Argus.

There were no deaths in either the study or control groups during the investigation. In fact, it

would take a very large multicenter clinical trial to reliably estimate the effects of different levels of each of the treatment actions on mortality. Had we those results it would have been possible to evaluate the therapeutic efficacy of Argus.

It is not unusual for unanswered and deep medical questions to intrude upon the evaluation of medical technology. Our only choice as designers of such equipment is to assume that current views about "good medical practice" are valid, but be alert to the results of clinical research that may change these views. Computer monitoring in the CCU has grown into a substantial industry since 1969, now exceeding \$100 million per year world wide. We still have no scientific evaluation of the therapeutic efficacy of such systems, but the clinical judgement of CCU directors seems to be that the systems help their staff deliver high-quality medical care.

Ambulatory Monitoring of Electrocardiographic Rhythms

Portable recorders became available in the 1960s, designed to store twenty-four hours of an ambulatory patient's electrocardiogram on a single tape. The job of analyzing these tapes became a growing burden to clinical investigators and the new rhythm monitoring algorithms developed for the CCU seemed an obvious solution to the problem. Thus, in 1971, we began to develop a high-speed version of Argus to analyze monitoring tapes for a project on the relationship of ventricular arrhythmias to sudden death in ambulatory survivors of myocardial infarction.

Argus needed to be speeded up considerably, since we wished to analyze the tape recordings at 60 times faster than their recording speed. One hour of the patient's ECG would be analyzed in one minute of processing time. It took many years to reach this goal, with part of the increase in speed coming from faster equipment and part coming from algorithmic improvements. In the early 1970s Floyd Nolle, Dieter Ambos and Ken Clark did most of the software and hardware development toward this goal. Charles Oliver led a clinical team that organized the patients to be studied and analyzed the data produced by our high-speed version of Argus.

Floyd was trying to organize the ECG patterns for many different types of heart beats into families with similar characteristics [17], [19].

He used a stick figure that summarized the several features extracted from each ECG pattern. The walls and desk in our office at the CCU were covered with plotter output showing the seemingly infinite variety of these stick figures. His observation that it would be much easier to teach a pigeon to recognize these stick figures than it would be to program a computer to do the job was immediately recognized by Ken and Dieter as a rare opportunity.

They investigated a suburban pigeonry and found the proprietor had two classes of homing pigeons, one at \$2 and a second class at \$0.50 each. The difference was that the \$2 birds would return to the pigeonry in suburban St. Louis and the cheaper birds returned to Crystal City, about 50 miles to the south. They purchased one of the economy birds.

Floyd tended to the pigeon during the week and my secretary, Shirley Gonzalez-Rubio took care of it over the weekend. It did not learn to recognize stick figures, it did provide a good bit of comic relief flapping around BCL's basement and Shirley's bathroom, and perhaps it gave Floyd some new ideas for algorithms before it was released to find its way back to Crystal City, where we assume it lived in Argus-free bliss ever after.

In the fall of 1972, Charles Feldman, of Worcester Polytechnic Institute, organized an Evaluation Group for Arrhythmia Detectors (EGAD) at the Dallas meeting of the American Heart Association. The purpose of this organization was to try to set up methods and procedures to assist in the objective evaluation of the growing number of computer-based arrhythmia detection systems. I was happy to place the resources of BCL behind this project because of its importance to the systematic development of the field.

It was to take more than a decade, but finally in 1984, Russ Hermes of BCL completed the last of a set of carefully annotated digital tapes for commercial sale to arrhythmia system developers [20]. Known as the AHA database, it had the benefit of careful review and annotation by some of the nation's most prestigious electrocardiographers. The effect of this database and its companion from MIT [21] were to bring research and development in arrhythmia detectors from a state of chaos to one of cooperative

progress. With an objective method to compare the performance of detection systems, it became much easier to recognize which methods were successful and which were not. A convergence on the successful methods ensued and the value of this kind of database in pattern recognition problems was demonstrated once again. The development of the AHA database was an important factor in improving the performance of several commercially-available, high-speed analysis systems for ambulatory ECG recordings.

Conclusion

Hal Davis has retired, and at ninety-one continues to receive the scientific acclaim he so richly deserves. Don Glaeser, Floyd Nolle and Maynard Engebretson, the three graduate students who helped me form BCL, went on to their doctorates through their work at BCL and then to highly productive careers in biomedical computing. Bill Gerth recently left St. Louis to join the family business in Nashville. Ken Clark and Russ Hermes are stalwarts at BCL. Dieter Ambos is a Research Associate Professor at Washington University. Wes Clark left Washington University in 1972 and was succeeded as Director of the Computer Systems Laboratory by Charlie Molnar. In 1984, Charlie founded and became the first director of the Institute for Biomedical Computing, which brought the two sister laboratories together within a single organization.

My years at CID and BCL were certainly exciting. I was privileged to be a part of it and to have had the friendship and support of those mentioned in these few stories and the many more who over the years have helped in important ways. I do not have any important wisdom to impart. Maybe it is worthwhile to say that perseverance and getting down to basics should be valued more than they are. It often seemed that we should abandon a research direction because other laboratories elsewhere were doing astonishing work, but in the end we persevered and nothing seems to endure like endurance.

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I also want to acknowledge the work of many friends and colleagues at CID and BCL not associated with the topics covered in these reflections. Because of the limitations of my title and a requirement for some restraint with respect to space, I have had to skip over many whose contributions to projects that I directed were significant. Of those not mentioned, I must recognize four special friends from the BCL years: Lew Thomas, who took over the laboratory when I went to Computer Science; Don Snyder, who taught me about point processes and much more; Jim Blaine, who worked closely with me from the time he came to BCL in 1967 until the present; and Virginia Bixon, who as laboratory business manager, has kept us all out of financial mischief.

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Perspectives Over Forty Years

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It has been said by some psychiatrists that there are just three categories of patients - "Poor me", "If it weren't for him or if it weren't for her", "change that kid, but don't change me". Well, when it comes to thinking about the past, each of us falls into one of another 3 categories. Of all the tapes we have in our memory banks, there are those who play only the bitter stories and the sad music, there are those who play only the triumphs, big or small, and the happy tunes, and there are those - and they are very rare - who play a balanced sample with an amazing objectivity and calm. And of course, we all occasionally play a tape that got into the collection by way of our imagination, not through any reality that anyone else can recall. The lost or messed-up tapes never get played at all. For after all, as Santanyana has said, for most of us, going through life is a slow movement from the forgotten to the unexpected.

Recognizing these ways in which we all function, I thought the best thing for me to do is to structure my recollections around a series of beliefs - those that I had when I entered medical school in the early 1940's and the parallel and very different set that I hold now in 1987. After I do this, I shall try to describe and explain some of the events that led to the changes. I shall conclude with some implications of these changes.

1. As I entered medical school I believed that a core of knowledge must be taught and memorized. I now believe that a core of behavior, not a core of knowledge must be inculcated. A person must be thorough, reliable, capable of defending the logic of his actions, and efficient in completing the tasks for which he or she is responsible.

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2. I once believed it was possible to recall and process all the necessary variables at the bedside or in the clinic at the time of clinical action after one had mastered a core of knowledge. I now believe that we need electronic extensions of the human memory and analytical capacity at the time of action just as we need X-Rays to extend the human eyes. Physicians should rely on such tools just as a traveler relies on maps instead of memorizing trips in geography courses. Faculties and researchers should keep the tools up to date.

3. I once believed that passing National Board and Specialty Board examinations could be used as an indicator of one's capacity to fulfill responsibility to patients over a lifetime. I now believe that good medical practice can only be assured through random audit of performance in the real world and that such an audit requires a defined system of care and the availability of up-to-date information tools.

4. I once believed that you could divide knowledge up into academic packages - courses - and that defects in performance such as unethical behavior could be remedied by adding a new course to the curriculum. I now believe that real problems in the real world - practical or theoretical problems - do not fit neatly into academic boundaries, and it is dangerous for professions serving real people to try to do so. Defects in the care process should be corrected either by up-dating the information tools provided for use at the time of care or by demanding a more disciplined use of the proper tools at the time of action. What is in the information tools will be determined by what the problem requires, regardless of the old classification systems for knowledge such as science, humanities, ethics etc.

5. I once believed that physicians should be the principal force in choosing among diagnostic and therapeutic options for the patients. I now believe that the patients themselves and their families should be the principal force and that they should always have a copy of their own problem-oriented records and use the up-to-date information tools in partnership with all medical personnel.

Let me go back 40 years and consider what might have led to these changes. The thing I most remember about those early years is not the actual material that we had to memorize, but simply the fact that we had so much to memorize - so much to regurgitate - so much to forget. Life for those first two years was a series of weekly quizzes, monthly exams and finals in biochemistry, anatomy, physiology etc - the so-called basic sciences. Who could ever forget those after-lunch, numbing sessions in darkened lecture halls when neuroanatomy cross-section lantern slides went on day after day? Long after the details on those slides have been forgotten, stories about the experience remain forever. A friend told me that one day in his school he was wakened from a heavy sleep in just such a lecture by the crash of a student's body hitting the floor of the upper tier aisle of a steep old fashioned lecture hall. The side of his chair had broken, and the #8 billiard ball that he carried, as Linus carried his blanket, slipped from his hand and noisily went step by step to the feet of the elderly lecturer. As the whole class came out of its postprandial nap, the droning old professor went over and turned on the lights, bent over and picked up the billiard ball, and said with his thin, elderly, high pitched voice, and with a rare wit that up until now had been hidden from the students, "Would the gentleman who just lost his head, kindly retrieve it."

And the memory game did not stop when we reached the clinical years. Anecdotes about feats of memory or embarrassing failures of memory were standard fare at the dinner table or in dormitory bull sessions. We were all so impressed when Dr. Loeb would walk on to a ward, see the face of a recently admitted patient, immediately recall her name and say her BUN in 1938 was 87 or some equally precise figure. And how vividly I remember the presentations we were expected to give from memory. One night I was up all night working up two new patients who were very sick and had very thick old charts. I knew I would have to present to Dr. Loeb the next morning on metabolism rounds - I would have to say all the right things - say them from memory and not take too long. Tony, my patient, was in his teens, had Addison's disease, was in an impending crisis. I began my presentation with: "Tony's disease began in early childhood, the pigmentation first being noted at age 7" - at which point that familiar voice of Dr. Loeb interrupted, saying "Weed, are you sure it was not at age 5?". You can imagine what that did to the programs and the files that I carried in my little personal computer of the 1940's - that little weary, up-all-night brain. The programs and the files were pretty messy to begin with - but after that interruption they were chaotic. It seemed that no debugging operation known to man could save the situation. But I did pull myself together and say, "Well sir, I am sure I could be

wrong, but age 7 must be somewhere in those thick charts - I would not just fabricate a figure for a presentation. Should we take the time to stop here and look through them?" Dr. Loeb said - "Well, Weed, that would take a lot of time and I am not sure that is necessary." At that point a demon -indeed the devil himself -entered my weary, exhausted mind and body and I said, "I have an idea Dr. Loeb. Let us ask Tony -he has heard his presentation so many times after so many admissions" - at which point that unforgettable smile of Dr. Loeb's came across his face and he exclaimed "Darn good idea Weed" and he turned to Tony and asked him, "When did your skin start to get darker?" The answer was wonderful. Tony looked up, and with an unforgettable smile of his own, he said "It began somewhere between the ages of 4 and 8." That broke up the assembled entourage, and Dr. Loeb said without hesitation, "We shall proceed; that point will not be pursued further."

I could go on for the rest of the evening with anecdotes over the next forty years in seven different medical schools. But the striking thing in those early years was the almost total lack of discussion of the very nature of the vast reservoir of medical knowledge itself. How should its boundaries be defined, what should be put into courses, and what was the evidence that what had been chosen for courses actually related in rigorous ways to the care of patients - and even if it did, what evidence was there that our tired and bewildered minds could recall and process the almost infinite variety of facts and variables that highly specialized faculty members were forever pouring into our brains. How come we had a "basic science course" in biochemistry filled with intricate details about Krebs's cycle, but we had no such course in basic psychology, when many, if not the majority of our patients, to say nothing of many of the students and faculty themselves, were beset with psychological problems. Think of how devastating it would be to the whole curriculum and all its pretentious Board exams as a basis for licensure, if the students were reading papers by Tversky, et. al. and Kern, et. al. and books such as that of Wason and Johnson-Laird, in which the following findings were neatly documented: 1. The human mind will start generating hypotheses in the earliest moments of encounters with patients and thereby prematurely bias the remaining steps in the search for data. 2. The mind will limit the number of hypotheses it generates to a number far smaller than the problem requires. We therefore do not fulfill our responsibility to the patients with the rare disorders. As Wason and Johnson-Laird state: "When the individual mind's logical ability is restricted, it will operate within heuristic or hit or miss procedures which do not guarantee a solution." 3. The mind will underestimate the complexity of problems and it will overinterpret the data it does collect. It will indulge in the categorical

reasoning of the expert. 4. The mind will take the probability information based on the studies of a very limited number of variables on large populations and let it supersede highly improbable but correct information on a very large number of variables on a unique patient, thereby often getting the patient into trouble. The mind also applies inappropriate prevalence data in many of its calculations, placing a patina of quantitative and numerical respectability on to a not-so-respectable foundation of misguided and inaccurate estimations.

As Wason and Johnson-Laird have said: "We like to think the educated human mind is capable of thinking in terms of propositions which take into account the possible and the hypothetical, and that the mind will be able to isolate the variables in the problem and subject them to combinatorial analysis which nicely exhausts the possibilities". But this of course as Wason et al point out, is exactly what most of their subjects failed to do.

And even more devastating to a curriculum committee would be to have one of their meetings interrupted by a poet coming back to life and reading one of her sonnets. Edna St. Vincent Millay wrote long ago:

Upon this age that never speaks its mind,
This furtive age, this age endowed with power
To wake the moon with footsteps, fit an oar
Into the rowlocks of the wind, and find
What swims before its prow, what swirls behind -
Upon this gifted age, in its dark hour,
Rains from the sky a meteoric shower
Of facts ... they lie unquestioned, uncombined.
Wisdom enough to leech us of our ill
Is daily spun, but there exists no loom
To weave it into a fabric.

Nor was anyone in the medical school ever suggesting that what the Tillichs and the Niebuhrs and even the Norman Vincent Peales were, in those days, saying in a different part of town, may have as much to do with understanding the medical plight of our patients as anything that PhD's in anatomy and physiology were saying.

We were so busy memorizing and regurgitating - going over hurdle after hurdle - that there was no time left to reflect and think philosophically about the system we found ourselves in. We were so consumed with doing the thing right, that we had neither the time nor the courage to ask "Are we doing the right thing?" Indeed, the basic premises that underlie most human endeavors are rarely surfaced and brought into question until there is a crisis. Our instinct for survival under somebody else's rules and our capacity for compartmentalization in our tired minds is phenomenal. Nor were the premedical years, in even the best colleges, considered a golden opportunity to think about what the practice of medicine was all about.

Pre-medical students seemed almost more consumed by mindless preoccupation with high grades in chemistry and biology prerequisites than were the sheep-like unquestioning medical students. One can only speculate as to what would have been the effect if a literature professor in college had said: "All pre-meds must write an essay on the following passage from Tolstoi's 'War and Peace' - discussing how it may relate to what pre-medical students are studying in college and what it means about the medical profession itself."

"She could not eat or sleep, grew visibly thinner, coughed, and as the doctors made them feel, was in danger. They could not think of anything but how to help her. Doctors came to see her singly and in consultation, talked much in French, German and Latin, blamed one another, and prescribed a great variety of medicines for all the disease known to them, but the simple fact never occurred to any of them, that they could not know the disease that Natasha was suffering from, as no disease suffered by a live man can be known, for every living person has his own peculiar, personal, novel, complicated disease unknown to medicine - not a disease of the lungs, liver, skin, heart, nerves, and so on, mentioned in medical books, but a disease consisting of one of the innumerable combinations of the maladies of those organs. This simple thought cannot occur to the doctors, as it cannot to the wizard who is unable to work his charms."

I was one of those highly compartmentalized medical students. When, I have often asked myself, did my vague unease with the system begin to crystalize into sharp and clear perceptions? In that first very unhappy year of medical school, I remarked to Dr. Sherry Washburn, the distinguished physical anthropologist and at that time one of our anatomy teachers, that I wish I could work with real tissues that were not some hardened-with-formalin cadaver, and take Callender's Surgical Anatomy book and just do operations - take out kidneys, etc. so I could get a feel for the real thing. He found me a little room, and he would give me leftover cats and dogs and an occasional primate left over from on-going experiments in departments in the medical school and university. It saved my life. At least for part of the day I was in the driver's seat - not a slave to the syllabi and schedules of a content driven basic science faculty. He then asked me to help teach the human anatomy part of an anthropology course he was to give that summer. I was determined that I would not make others suffer the way I had felt I was suffering in that first year in medical school. The first thing I did was to tell the students that no one should buy a book until I gave the go-ahead. I then showed each individually how to use a scalpel, what arteries, veins, muscles, and nerves and visceral organs looked like - and then said make believe you are Vesalius - begin to dissect and explore - putting your own names on things and guessing what the

functions of a given muscle might be. After a few weeks had gone by and they were intellectually in charge of their own situations, I said, "Now buy a book and see what Spalteholz or some other great anatomist thinks". It was at that point that I was beginning to realize that the first two years of medical school were so devastating because one was forever memorizing observations which one had never made and memorizing answers to questions which one had never asked. Years were to go by before I realized how toxic to the healthy mind memory-based credentialing systems can be. For many medical students, the damage seems almost irreversible. Indeed, it was at the end of that summer during the war that I thought of leaving medical school, but I was in a Navy program and the officer in charge said, "We have reviewed your college record; you are capable of meeting the requirements. Stop bitching and get to work. If you flunk out I personally shall see that you shall not follow your brother and your father to the Far Eastern theater of war, but you will wash dishes in the Brooklyn Navy Yard or be tied to a desk in some recruiting station in the Bronx. And so I labored on.

After several clinical years I wanted to try my hand at some basic research in biochemistry - particularly in nucleic acid chemistry. I went to Dr. Palmer, the Chief of Medicine at Columbia at the time, and we talked about the great things going on in the biochemistry department at the University of Pennsylvania. He said he would call Dr. Wilson (the department chairman) and recommend me, but they may want me to do nothing but biochemistry - no dabbling a day a week in the clinic or running off to Grand rounds. "You know", Dr. Palmer said to me, "the sad part about all this is, if you are very good in research you will probably never come back to clinical medicine, and if you are bad or mediocre you will come back - so sometimes I am not so sure about the end result of such recommendations" - but, nevertheless, he got me settled in that land where the great Meyerhof was still giving seminars, the new isotope methods were opening up all sorts of exciting matters in intermediary metabolism, and best of all, the very character and integrity of Dr. Wilson himself permeated the atmosphere of the lab I worked in. I learned then that ethics is not a series of abstractions in some course, but it is what you feel and hear and see among your leaders as you work every day.

It was in this period, when I was working day after day with PhD's and graduate students in biochemistry that I began to see the world in a very different way than I had seen it as a medical student. These people worked on one or two problems at a time - they lived and breathed a single problem - they read extensively about the problem - they wrote papers on it. In their lives, time and tasks were variables and

achievement the constant. 1 or 2 tasks at a time - and the necessary time and grant money were made available until peers reviewed the work and it was published. In contrast a doctor or a medical student did not have one problem - one patient could have five problems and there were thirty patients on the ward and hundreds on the rolls of the clinic. Time was not set by the doctor - the appendix would perforate on its timetable, not the doctor's. There was nothing in the life of the Ph.D that would equip him to prepare medical students for a world of multiple tasks in limited time with widely varying levels of achievement, with the lives and comfort of real human beings involved at every step. Basic science faculty had been led to believe that somehow, if they could just get the facts into a medical student's head, he would always be able to recall them and would be able to integrate them properly into the complex problem situations that he would confront day after day. The medical students were being stuffed with the facts of basic science, but could it be that the behavior of a scientist was escaping them - indeed would it not be impossible for anyone to exhibit good scientific behavior under the conditions of modern medical education - multiple PhD's and MD's converging on the single mind of medical student - all under the premise that a mind so exposed could store, recall and process all the appropriate variables at the time of problem solving in the real world.

Medical education and care, with their Board exams and licenses based upon them, were also contradictory to the world of the professional musician, the professional athlete, the vigorous business man, or the research scientist. For them, quality has always been defined as the excellence with which a well defined function is performed. In medicine quality has been defined as that which people with credentials do, and only others with credentials have a right to judge it - even though everyone knows those credentials may represent nothing more than a passing grade on an examination taken many years ago. Furthermore, examination results had never been shown to consistently reveal what the examinee would do when confronted with a real problem in the real world under all sorts of conditions. Suppose some regulatory agency had scrutinized the credentialing process of the human mind with the same rigor that the Food and Drug Administration looks at a new drug or a new instrument. Had they done so they would have found that the production standards and the requirements for on-going quality control of the output of the credentialed human mind are far below any standards we use for any drug or instrument. How ironic, for it is the "educated, credentialed" human mind that orders the drugs and makes all the decisions that set all the various technologies into motion.

Thoughts similar to the above came to me

with a special force after finishing my time in biochemistry at Penn and after a stay in the Army and clinical time at Johns Hopkins. In a joint appointment in pharmacology and medicine at Yale I lived in three worlds: the world of clinical medicine, the world of nucleic acid research, and the world of teaching the endless details about drugs to medical students. On one occasion, after dumping a particularly large load of pharmacology details on the heads of the second year class, my mind, without warning, brought to the surface recollections from George Eliot's Middlemarch. In a small English town, there was this lovely young girl who aspired to higher things, and, to her, an opportunity to assist and work with the local scholarly bachelor, Mr. Casaubon, was everything an ambitious young lady could hope for. He had a large house, a large library, and many scholarly pursuits. He was always working on his store of knowledge and was in Eliot's words "as genuine a character as any ruminant animal, and he had not actively assisted in creating any illusions about himself". Eventually, as they worked together, the less scholarly aspects of Mr. Casaubon's physiology were awakened, a courtship ensued and marriage took place. And it was several weeks after the marriage that, in Eliot's words, "Dorothea had not distinctly observed but felt with a stifling depression, that the large vistas and wide fresh air which she had dreamed of finding in her husband's mind were replaced by anterooms and winding passages which seemed to lead nowhither". Were the minds of these medical students just mindlessly collecting undigested facts in dim dark corridors that would lead to nowhere - nowhere but to depression and bad habits of thought? What was I doing to the students' minds? What would their minds eventually do to the patients? Was this all educational malpractice that someday would lead to medical malpractice, with the students becoming the ultimate victims and we the faculty getting off, not only unharmed, but totally unaware that we were the root of the problem?

And from that world of teaching facts, one day I walked on to the ward as an attending physician and said "Do not present a new case in the usual fashion. I want to know where we stand on each of the problems we discussed on my last visit - and be like a good graduate student, bring me your manuscript and notebooks - I want to see the problems, the data, and the conclusions and all subsequent actions on the problems." "What notebook", they asked. And I said, "your notebook must be the patients chart. Bring it to me - the chart on the patient we discussed last time." And suddenly I realized that there is no complete list of problems, just a few "Impressions" written on the night of admission and never up-dated. The plans we had discussed on the previous visit were not unambiguously recorded for each problem and there were no problem-oriented progress notes and no flow

sheets to reveal to us the logic and the results of what we as doctors and scientists were trying to do. How could we define quality as the excellence with which a well defined function is performed when we never defined clearly what medical care should be - how defined and how recorded. We simply measured what people knew on an arbitrary exam at one moment in time and equated it with good care over a lifetime and gave the person a license.

And so I left Yale to become the Director of Medical Education at the Eastern Maine General Hospital in Bangor, Maine. The first order of business was to develop a problem-oriented medical record as the very basis for treating an intern as a graduate student. The second chore was to get an adequate library so that the physicians could look things up when they did not know. And my job was to be the reader and the auditor of the records - the scientific manuscripts that represented the efforts in medical care. We would no longer teach a core of knowledge - we would teach a core of behavior - was the physician thorough (was the data base defined and complete, was every problem on the list, was there a plan for each the problems, and did progress notes, titled with a specific problem, show that the plan was carried out? Was the physician reliable - were the findings in the chart accurate? Was the physician analytically sound - could he defend every plan within the context of the other problems and with references or common knowledge in the basic sciences? As the actual data unfolded in the progress notes and on the flow sheets, did the physician draw logical conclusions and make reasonable adjustments? Was the physician efficient as he cared for the patients in such a defined system?

No matter where I went in American medicine, from the most prestigious medical centers to the most isolated solo physician, we found that few could meet the standards that their credentials suggested and that a well defined system of problem-oriented care required. Memory-based, credentialed specialists had become Chairmen of departments and Deans, they had formed their own fiefdoms with their own provincial ways of keeping records, setting fees, and teaching students and residents. To this day, most of them have not worked together to establish a single, problem-oriented, computerized medical record system throughout an institution and a community, with the patient, at all times, having a copy of that record in his or her own hands. It is like the situation that existed over a century and a half ago when the great railroad barons and tycoons had trouble agreeing on a single gauge track that would have effected enormous efficiencies in the transportation of all sorts of materials over a broad geographic area. But it was with just such a grand scheme in mind, that we undertook the development of the PROMIS

computerized system to support the human memory and to help in the coordination of the many providers working on a single case. And the PROMIS system soon revealed that when you solve the memory problem of the human mind, you uncover a processing limitation that is even worse than the memory limitation. That is to say, with 55,000 displays of medical details instantly available at the doctor's fingertips, he could be overwhelmed by the task of integrating the relevant details from the unique patient with the relevant details now so instantly available to him on a computer screen. We came face to face with the realities and complexities in decision making that had been hidden under terms such as "clinical judgement" and "intuition" and "experience". The hallucinatory fulfillment for students and faculty alike was rudely interrupted.

We all knew in a common sense way that decisions could go wrong if you were making them without enough information to start with or if the so-called facts in the situation were not accurate. The decision could also go wrong if one did not know how to interpret the facts. Medical training, as most of us had known it, had not equipped us to come to terms with this difficult situation. Some turned to mathematicians, psychologists, and computer scientists for help. Many of those people, in turn, focused mainly on the intelligent manipulation of the facts that their medical colleagues gave to them - paying little attention to the inaccuracy and incompleteness and highly provincial nature of the data that was flowing from a deeply flawed medical care system. The data came from a memory-based, credential oriented, group of medical providers - many of whom were specialists who were not linked to one another in a highly disciplined fashion and who, in many cases kept sloppy medical records. Such records and a medical literature system that has been severely criticized for its lack of quality control standards have been the underlying basis for their "expert" opinions and uninhibited intuitive leaps to conclusions about diagnoses and management options. All of this has led to much magnificent navigation to the wrong port. There were calculations of probabilities before many relevant and easily available variables had been isolated and taken into account. There seemed to be a disregard of the idea that one uses probabilities in direct proportion to one's ignorance of the uniqueness of the situation. Combinatorial thinking, on the other hand, that seeks out the uniqueness of a situation and that exhausts all the possibilities in a complex diagnostic or management situation is as much beyond the unaided mind as modern astronomy is beyond the human unaided eye. And yet here we were in 1987 still examining students on what they know instead of on how gracefully and effectively they interface with the areas of their ignorance when others are trusting them to solve a problem.

Patients are not interested in what is probable among large numbers of patients based on a few variables - nor are they interested primarily in what the expert knows - they are interested in what is wrong with them - no matter how improbable and unique their situation might be. And knowing the power of uniqueness in making wise choices among diagnostic and management options, we realize how serious have been the consequences of our neglect of all the details in the complex lives of patients - how easy it was to operate on a meager set of facts that we could hold in the memory or elicit from an incomplete and disorganized medical record. And how easy it was to neglect the patient's role in his own behalf. If the patient and the families do not understand and do not have the right tools to work with, then the most sophisticated efforts in the information sciences may come to naught.

In that regard, I remember one day when I was the attending physician on the computerized ward with all the displays and incredible electronic linkages to other services, they wanted to present a patient to me. I said, "Do not present a new patient; tell me who is going home today. The nurse volunteered the name of a middle aged woman who had lupus for 10 years. I suggested they give me 15 minutes with the patient and then they could return for discussion. I asked the patient to tell me all she knew about each of her problems. She knew very little.

"Do you have a copy of your own medical record?" "No."

"Are all your medications in the bedside stand, and does the nurse come around at regular intervals to see if you are taking the right ones at the right time?" "No. The nurse just comes with little paper cups with pills in them and I swallow whatever is there."

"Do you know what a flow sheet is - what parameters we are trying to follow - what end-points we are trying to reach?" "No."

At this point I called the staff back together and told them what I had found. Their reactions were:

"We never give patients their records."

"We do not have the time to give medicine that way and besides it would not be safe to leave her with them unattended - she is on many powerful drugs."

"The patient is not very well educated and I do not think she could do all the things your questions imply."

"But," I said, "you said she is going home. She lives alone. At 2 PM you will put her in a wheel chair, give her a paper bag full of drugs and send her out the door. Are you going home with her?"

"NO. Is her management at home our problem?"

"You just said she could not handle it - who will do it? The patient may not be very well educated or very bright - but how could anything be more stupid than what we are doing?"

We must think of the whole information system and not just infinitely elaborate on the parts that interest us or fit a given specialty. Patients do not specialize and they or their families are in charge of all of the relevant variables - they are the most neglected source of better quality and savings in the whole health care system. After all:

1. they are highly motivated (and if they are not, nothing works in the long run anyway)
2. they do not charge, they even pay to help
3. there is one for every member of the population.

In the time remaining, we could go into greater depth on any one of the aspects mentioned above or on the details of how a "knowledge coupling" system was developed on microcomputers for overcoming the "voltage drop" from the best that is known for solving a specific problem to what is actually done for the average patient on the average encounter in American medicine. There has already been enough experience with the new tools in medical practice to show that they are practical and that it is realistic to operate under new premises. But I would like to use the remaining time to reflect on the devastating effects of the wrong premises of the educational system, discuss how the present situation may have evolved, and how new premises and new information tools can extricate us from the extraordinary difficulties we now find ourselves in.

First of all, the evils of a memory based system. Since knowledge is forever expanding and since each specialist is bent on stuffing everything he knows into the students when he has them, the student has no opportunity to think about the nature of the task - the nature of the knowledge and the results of its usage. The student is literally consumed by the process of memorizing and regurgitating. It is as if all travelers must have a degree in geography, must have sat through lectures by specialists on every geographic region, and must travel from memory and have credentials based on passing exams on the territory they want to travel over. But the real world of transportation is not that way. Everyone can travel anywhere with a set of maps, minimal background and no credentials. As I think back upon my own early days in medicine, I am horrified not only at how much I was prisoner of conventional wisdom, but also how unaware I was of the arbitrary nature and inherent ambiguities in much of what I was required to learn. Nor was I aware of how arbitrary were the boundaries between

what I was preparing for and what others were doing in many other fields. For example,, as a student when we use to work over the CPC's in the New England Journal, week after week, no one told me, nor did I discover on my own, that the great Dr. Cabot who started them also wrote a book in 1926 entitled "The Adventures on the Borderland of Ethics". In 1931 he was elected the president of the National Conference on Social work and in 1933 he wrote on the "The meaning of Right and Wrong" and in 1938 a book entitled "Honesty". And of course Dr. Cabot can never know that a half a century later President Bok of Harvard could be lamenting, in his article "Needed; a New Curriculum" that a study of 400 medical students showed 88% admitted having cheated at least once during college.

Among all the books that had been assigned to me, there was not included a little book called "A Study in Hospital Efficiency" by E.A. Codman. We as medical students had no way of knowing that a physician up in Boston had written 25 years earlier about all the problems that were bothering us - and furthermore, he was offering some very concrete solutions. He stated at that time, "It is not idle to say that we have not already much truth at our disposal, but it can be said that we should find more truthful ways in which to use it". Not only was his book not known to the medical students, it was not in a standard publication. He had to publish it himself, and his reasons for having to do so tell us much about the problems he faced with the university, the journals and the hospitals. In that day, medical students were insulated from the political controversies that swirled around them, and they are insulated today. And that insulation will continue as long as the students are burdened with courses, computer simulations of, and examinations on accumulated wisdom. Only real and current problems, honestly confronted, can immunize the students against the misconceptions and generalizations of those who teach. And like all immunizations, they only work if you get there before the invasion and the damage have taken place.

As a medical student I never gave a thought to the nature of medical knowledge - the epistemology that was the basis of my whole career. In the whole matter of making a diagnosis, I never reflected much on the word itself - that it involved just a specialized classification system, and that great minds had struggled for decades, even hundreds of years over the underlying principles of taxonomy - the science of classifying things. I passed my organic chemistry in college by memorizing and regurgitating a few formulas, but the whole field of evolutionary biology escaped me. Not only had I not read Darwin's musings in a very thoughtful manner, but in later years I was not reading authors like Sokal and Sneath, numerical taxonomists who were

saying "It is the self reinforcing circular arguments used to establish categories, which on repeated application invest the latter with the appearance of possessing objective and definable reality. This type of reasoning is, of course, not restricted to taxonomy - but it is no less fallacious on that account. --- A group assumes a degree of permanence and reality quite out of keeping with the tentative basis on which it was established." No medical student in our present system would have the time, the background, the wit and the courage to say to an expert diagnostician, "By calling your manner of diagnosis or classification an art, rather than a science, you are defining the problem (of diagnosing and categorizing) out of existence."

Medical students are made to feel stupid, and patients overhear themselves being identified as "turkeys" or "neurotic" when they struggle with the inconsistencies among experts and the variance of their unique situation from textbook averages and from the mathematical manipulations that were based on flawed premises and inadequate or unreliable data. In our training, we were always so busy meeting the demands of superiors, made according to their beliefs, that we never read about the history of people like Codman and the Mayo brothers who were locking horns with prestigious medical schools and the organized hierarchies of American medicine. We never demanded logical and rigorous connections between what we were memorizing and what we would someday do in the total context of patients' lives. We just assumed that somehow a complete and evenly working system would evolve out of a group of scientists and specialists of all sorts making their living out of their chosen specialized part of the human body. It should have been in the middle of our medical development, instead of alone in some forgotten college course, that we should have heard the cynical belief of Malthus that we would always be victims of the insensible bias of situation and interest. Medicine has had, and will always have, its counterparts to the Jay Goulds, the Andrew Carnegies and the Whitneys of the business world. They had, and physicians have, their apologists who translate unconscionable, even cut-throat behaviors and unbalanced distribution of resources and rewards into words and phrases like thrift, dedication and pure science. All people in medicine are subject to that passion which Karl Marx said was among the most violent to inhabit the human breast - the passion of self interest. As we now grapple with the relevance of the productive efforts of each of us as individuals to the whole health care enterprise with all of its humanitarian and scientific aspects, it is in the articulation and creation of information systems that all the pieces can be brought together into a meaningful whole. Up until now much of the prestige and even financial reward have been related to the science of disease and specialized approaches to

disease. A rigorous and highly coordinated information system can now challenge the best minds to focus on the science of medical practice. John Stuart Mill has said that it is production only that is the true province of economists and planners and that distribution and consumption of the wealth is not really in the long run in our hands. But with the power of modern information systems to couple the best knowledge to everyday actions, every part of the system can be related to every other part. The loop can be completed. We no longer need to be in Le Corbusier's phrase, "A spectacle of fragments of intention". We are now in a position to move much of medicine from the philosopher Karl Popper's World 2 to his World 3 - from the world of our notions, our intuitions, our judgments, our mystique to a world of objective reality that is open to criticism and logical correction of defects as they appear. Memory based, credential-oriented systems, with their "habits of certainty" and obscure dark corners of mystique must now be abandoned. Compassionate concern without competence and accountability is always in danger of becoming fraud and malpractice.

Once we stop examining physicians on what they know and start examining them on how effectively they operate with modern information tools that have built into them the parameters of guidance and the currency of information for doing each job correctly in the context of an individual's life - then will we be able to return to that era of a century ago that Sloan the historian described - that era when moral philosophy was the most important course in the college curriculum. It was usually taught by the college president. In Sloan's words, "it was the capstone of the curriculum -- it aimed to pull together, to integrate, to give meaning and purpose to the student's entire college experience. Even more important, it sought to equip graduating seniors with the ethical sensitivity and insight needed to put their newly acquired knowledge to use in ways that would benefit themselves and the larger society... Intellectual unity was required as the essential safeguard against moral and cultural chaos". He quotes Horace Mann as saying that schools are "the balance wheel of the social machinery".

But what happened as the century came to a close and our own century began? Knowledge expanded, subject matter demanded to be included in the curriculum, and fragmentation was underway. You and I think of Adam Smith as the first great economist, but he was, first and foremost in his day, a professor of moral philosophy. In our time, his career and the courses he taught have splintered into political science, economics, philosophy, philosophical ethics, psychology, anthropology, and sociology. Fewer and fewer teachers could teach by the example of the breadth and moral concerns of their own lives. Sloan says, "Faculties

became trained experts. And emphasis on ethics gave way to an emphasis on research and specialized training". Scholarly productivity consumed us all. And now what are some of the products of that objective, scientific scholarly activity? We have a massive mixture of the good and the bad - thalidomide and penicillin, Three Mile Island and relativity, modern plastics and undrinkable water supplies.

If we are ever to recapture the intellectual unity that is the essential safeguard against moral and cultural chaos, and still not be nihilistic about the advancing technology and ever expanding knowledge we must change the premises of our educational system. The new tools for extending our minds at the time of action allow us to do that. But many of us just keep extolling the virtues of the modern information tools while we do nothing to change the premises that underlie the system in which they must operate. In many places, we have literally done little more than automate the chaos, or use the tools in ingenious ways to "pick up after" erratic unaided human minds as they set all sorts of misguided clinical activities into motion, instead of guiding the actions in the first place. Our very use of phrases like "expert systems" and "artificial intelligence" suggested to many that we had yet to admit that many experts and many an unaided intelligence cannot do what patients and third party payers had always assumed they could do.

Were I teaching biochemistry or microbiology with these new tools in place, I would not be overwhelming the student with tricky exams with multiple choice questions about a million possible metabolic pathways; but I would ask him to stand back and notice that a single *E. coli* can make all the vitamins and amino acids with just a little salt water and sugar thrown in, something that no human can do. I would also point out that the civilization of *E. coli* is not very sophisticated - just a division every 50 minutes. No single cell of a multicellular human being is so metabolically competent, yet together they have developed a higher organism which in turn has developed a higher civilization. As the cells came together to do bigger things, each gave up its autonomy in order to do its specialized functions better, but yet do them in the context of the other cells of the organism. Now the time has come to think in more precise terms about how the single cells of society, human individuals, communicate to accomplish larger goals. It is true that in this information age we hear a great deal about how the human memory, conscious analysis at the time of action, and verbal and scribbled words are not adequate to the task. But at the same time we are still tyrannizing students with premises and examinations and credentials that suggest that the human memory can retain all of the choices or options available for solving a problem, that it can on its own mobilize a

complete knowledge of the circumstances of the moment that are significant input for solving a problem, and that it can retain all the steps of analysis of the variables and implement those steps at the time of action. Complexity demands that one have the right combination of people, tools, and philosophy to deal with that complexity in an effective and productive manner. Whole systems must be thought out in advance. One individual cannot, all at the same time, be the cartographer who makes maps and the busy traveller who uses them. And in medicine, the options on the medical landscape must be laid out in great detail and then made available to patients and providers alike at the time of action. Modern knowledge coupling tools are now available to do that - we just must get on to using them. The expert cartographer cannot tell you what our trip should be - but neither can you make the best possible trip without his map. There are almost an infinite number of trips on the map, but each of them must be made within the restrictions of the rules of the road and the traveler's destination.

For society to grapple with its problems and with problem solving in all areas where complexity is overwhelming us, we need to evolve a nervous system that can precisely connect the parts - and that is exactly what our computer information systems are beginning to do. Ever since the stone age it has been extrasomatic evolution that has been important to us - we, as physical beings, have not changed that much. It has been the tools that man has been able to fashion that have been directly related to his progress. If the professors of moral philosophy of 150 years ago had our tools, they would have been able to master and control details and construct corrective feedback loops without being swallowed up by the ugly, non-cumulative, stultifying process of memorizing, regurgitating and forgetting - all in the name of higher education. We should at least call it lower education - reminding ourselves on a daily basis how backward we are. Students should be colleagues using these modern tools to build with us - recognizing by their daily efforts as John Dewey said, "There is an inseparable relationship between knowledge and action, research and its consequences, science and ethics, the natural world and human values". He proclaimed against the fallacy of selective emphasis.

We are now in a position to heed, in very specific ways, Whitehead when he said that it is a misconception, particularly among educated people, that you can think about what you are doing at the time you are doing it in a complex task, or that civilization rises in direct proportion to its capacity to put complex tasks at the unconscious level.

Let me now express some concluding thoughts. It is true, as Boorstin the historian has said, that often the enemy of new knowledge

is old knowledge - scholars who knew Ptolemy's maps had greater difficulty recognizing a new continent than those who had never learned that America could not be there. And since modern information tools can do things that the unaided human mind cannot do, when we use such tools we may see a picture of medicine that we have not seen before. The most experienced, the most highly credentialed "experts" may be the ones who find it most difficult to accept the new ambiguities and the contradictions to our present "knowledge". John Milton found it difficult to accept the telescope. It presented a picture of the universe different from his own. But the volume of knowledge is also one of its own worst enemies, if one has pride in knowledge - particularly too much pride in the knowing itself. For when one becomes proud of what he knows he is in danger of becoming imprisoned by the boundaries of what his limited human mind can know, and he does not get on to the business of building, and using consistently, the tools one needs to mobilize crucial knowledge at the time of problem solving in the real world. Never again should we judge people or empower people on the basis of what they know or once did know. We all should be judged on what we do. Nor should time and tasks be the constant and achievement the variable in education. Each human being is unique, and if each is to reach the highest level of achievement in what he does, then no two people can ever be expected to do the same number of tasks in the same amount of time to the same level of quality - and every individual should have at his disposal the best possible tools for doing one's work correctly.

Having changed basic premises and having introduced new tools, how then do we define a physician or a nurse? First of all, we should recognize that no one, no matter what the education, can acquire all possible technical skills in medicine, even if the best information tools are at one's fingertips. Nor can one be born with the patient, move out of town with the patient, or be available 24 hours a day, 7 days a week all year round. The care of a human being over time is the efforts of many people, and the patient or the family should have a central role in coordinating all care. Although we all recognize the evils of specialization, for many of the tasks in medicine to be done at a high level of quality there is no alternative. The problem has been that the efforts of specialists have not been coordinated and in the context of the whole life of an individual. As Wendell Berry has said in the context of farming, "Specialization is thus seen to be a way of institutionalizing, justifying, and paying for a calamitous disintegration and scattering-out of the various functions of character: workmanship, care, conscience, responsibility." Wendell Berry thinks of the modern one-crop farmer as an exploiter, whereas the old fashioned complete, ideal

farmer is a nurturer. For him the standard of the exploiter is efficiency, the standard of the nurturer is health - his land's health, his own, his family's, his community's, his country's. Our goal must be to develop a system of medical care whereby each individual is the "nurturer" of his own health care, and where he has available to him the guidance of an overall information system and the skills of the best trained specialists. Until such a framework is in place, and the patient is in charge, our situation can only grow worse. The exploitative nature of the specialist will get out of control. In Berry's terms, "The specialists are profiting too well from the symptoms to be concerned about cures (prevention of the situation in the first place). The problems become the stock in trade of specialists."

The time I had this evening is limited, and so I neglected many aspects of my experiences in biochemistry, internal medicine, and computerized problem oriented systems. As exciting and as profitable as many of the individual experiences were, it is my preoccupations with making the efforts of us all collaborative and cumulative that seems so important to me now. Once a defined system of medical care and education, based on a new set of premises, is in place, the following advantages may become apparent:

1. Patients and students will become productive members of the system as they move from a dependency state to informed partners in the process. The energy that went into memorizing and regurgitating can now go into thoughtful analysis, useful work, and suggested improvements in the system.
2. As Knowledge Couplers immediately map the patient's unique problem and situation against known diagnostic and management options, students and all providers will learn to ask the question: "How well do present arbitrarily defined classification systems and therapeutic interventions accommodate the unique combination of findings presented by the patient?". The focus will be as much on the fallibility and inadequacies of current knowledge as it will be on failures and inadequacies of patients and students.
3. Students and providers will shed their habits of certainty and associated intolerance, and cultivate instead a capacity to tolerate and to negotiate the ambiguities that inevitably appear when natural situations are honestly confronted. Each patient problem becomes a research challenge and not just another case to be run through the specialist's mill.
4. Creative people from all walks of life, as they interact with the medical care system, may offer very concrete suggestions for improving a given step in

the very well defined processes of care. No longer will improvement of the system be just the province of medical researchers and members of the medical industries.

5. Since everyone will eventually be an informed, knowledgeable member of the medical care system, priorities can be fairly set and the economics of care openly discussed. No economy would ever be able to support the expectation of the best of medical care for all people, in all age groups, at all times.

And finally, each year that goes by, one recognizes more and more what a tiny cog you are in this massive civilization of ours - and how dependent you are not only on those that surround you but those who preceded you. It is not possible to remember and recognize everyone who has had a share in even the smallest contribution. To try is to run the risk of some serious and crucial omissions. I would like to say, however, what a privilege it has been to have worked with so many dedicated and talented people over the years.

AN HISTORICAL PERSPECTIVE ON CLINICAL LABORATORY INFORMATION SYSTEMS

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SUMMARY

The clinical laboratory environment represents a microcosm in which practical solutions to operational problems in medical informatics have gone hand in hand with the development of laboratory instrumentation and computer technologies. These achievements follow a typical pattern in technological development, leading from the specific to the inclusive. The history of laboratory computing offers insights, not only for the past, but also for the future.

INTRODUCTION

I have been asked to present a history of laboratory information systems as one aspect of the short modern history of Medical Informatics. In this context, I must state my view that the key issues in the evolution of any technology cannot be captured by reciting a set of facts. Rather, as in the history of science, the turning points are related to insights - in this case insights into the logic of a particular kind of clinically related work - where the reward for understanding the process has been a good design as measured by the practical effectiveness of information use. This perspective suggests that there is an inverse to Gresham's law, in which good technology is presumed to drive out the bad through a marketplace of ideas tested by performance. For this interpretation, I am most directly indebted to Devendra Sahal and his *Patterns of Technological Innovation* [1] and to Richard Foster's *Innovation, the Attacker's Advantage* [2]. But the deepest support comes from Arnold Toynbee, who, in *A Study of History*, notes that "Technology is perhaps the one product of human activity in which there has been continuous progress." [3] It is, in some sense, a favored arena in which we have tenaciously held on to what we have learned.

Thus, like time's arrow, technology pushes us to fulfill the inscription above the National Archive: "What is Past is Prologue."

Underscoring that history need not face backward, Toynbee titles the last chapter of the last volume of *A Study of History*, "The Next Ledge," remarking that "The next ledge above, unlike the last ledge immediately below, is invisible to climbers who are striving to reach it." [4]

MOTIVATIONS AND MATERIALS

In laboratory information systems, and in medical informatics generally, we have climbed from ledge to ledge in the solution of demanding practical problems, but each discovery, once achieved, has almost immediately appeared obvious, so obvious, in fact, that these advances have generally escaped academic commentary and recognition.

The motivations for the climb have changed little in more than 20 years. The four reasons for automation, cited in the 1966 edition of the *Encyclopedia Britannica*, are the same today:

The decision to shift from manual to machine operation is usually determined by consideration of the following factors:

1. Saving of labor....
2. Saving of time....
3. Effects on personnel...[which may]... nullify anticipated savings in labor.
4. Need for accuracy.[5]

Furthermore, the same edition of the *Encyclopedia* commented on the critical role that computers were already playing in society:

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Electronic computers...have now become the commonplace tools in data processing for government, business, and industry; in scheduling and control of manufacturing operations; in military systems...; and in scientific activities.... A whole new profession has arisen - the art of using and applying computers to problems of all types. Most college and university students now receive some training in the design and use of computers, and science and mathematics curricula are being revised in the secondary (and even elementary) schools to introduce the new concepts required.[6]

To the engineer, the clinical laboratory is a light industry where measurements and observations are made on a patient's blood or other body fluids at a physician's request, and where the major visible products are the reports that contain these results. Addressing the issues of information automation in the early 1960s, laboratorians were not hampered by traditions and conventions from medicine's past because the clinical laboratory was coming into its own at the same time as the new computer technologies. Clinical laboratory science and the mechanization of laboratory measurement had progressed to a point where the challenge of computer automation was a natural extension of other developmental activities, so that laboratorians accepted the computer as another piece of instrumentation. They began by addressing problems that were close to the bench--data conversion from instrument data to clinical form and the calculation of measures such as standard error. Foresightful individuals, anticipating a flood of demand for new lab services, projected that computers would have broader uses in the organization, generation, and delivery of lab results. They were right. Today, a modern, fully featured system can handle an almost paperless flow of information throughout an entire laboratory complex. But such systems have more than 3,000 separate (and hard won) subroutines [7]! The dimensions of this problem were unsuspected by the pioneers.

PERSONNEL

In the 1960s, the idea of laboratory computer automation was "in the air", but an attempt to identify the first steps and who carried them out would probably lead to much irrelevant dispute. We now understand the many roots of this common endeavor, so that it is not surprising that, even at the beginning, the number of participants working on some aspect was very large. I will cite a few individuals whose energy and optimism will stand surrogate for all of the instrument automators, pattern recognizers, laboratory managers, medical technologists, vendors, programmers and users that led the way. At one time or another at the NIH: Williams, Cotlov, Brecher, Bull, Dutcher, Pratt, and Prewitt; in England: Whitehead; in the middle west: Hicks, Strandjord, Rappaport, Ditto, Lindberg, and Tong; and elsewhere: Seligsohn, Straumfjord, Steward, Krieg, Wattenberg, Mitchel, Peebles... and many others. Moreover, in technology, unlike science, major contributions are often both widely

distributed and nearly anonymous - a matter that has constantly plagued those with academic careers. Therefore it took foresightful academic chairmen like Benson and Hutchins and Lucas, thoughtful NIH policy advisors like Kinney, and NIH administrators such as Stone to provide a level of academic support that would allow the field to grow in conceptual stature as it grew pragmatically.

APPROACHES AND EARLY RESULTS

Because much initial work focused on issues close to instrumentation, the limited capacities of the LINC, the DEC PDP-4 through -8, the IBM 1800, and the early transistorized calculators such as those by WANG and OLIVETTI were the most immediate limits to be overcome. Adequate performance generally required writing in an assembly language. Distinct operating systems were the domain of large machines, and there were few software tools. Most on-line debugging consisted of reviewing and manipulating binary code in the registers of the machines themselves. To be successful at all, a programming solution had to be focused and specific.

Every area had its unique problems. Chemistry became absorbed in translating analog signals into digital measurements, and the Skeggs autoanalyzer presented the same "peak picking" measurement problems as were present in electrocardiography. Designers, who set about automating the task of counting blood cells under a microscope to create a differential white count, encountered the now familiar interface complexities associated with apparently simple professional tasks. The logic of cell recording by automated key pad was found to involve so many ins and outs that the process required a whole organization of its own. In cytology, the repetitious quality of observations focused attention on "canned" but modifiable reporting mechanisms, but brought up the linking of present specimens with past ones, and a cross linking to a surgical pathology data base. Although the blood bank could be formulated as an inventory problem, the medical requirements were found to be so very complex and dynamic that they could not be solved by off-the-shelf inventory ideas from industry. Microbiology was faced with linking multi-step diagnostic work sequences that extended over several days' time and with managing an encyclopedic set of bacterial alternatives with many potential synonyms and qualifications.

Immediate problems with machine capacity made it hard to appreciate the importance of unresolved issues involving human factors and medical logic. Each successful program offered the promise of a more general solution but as new areas were tried, the parochial nature of the initial approach became evident. A logic that functioned very well in one area, when tried in another, was often found to border on the absurd. Thus, for example, chemistry systems that started with a numeric base lacked a data structure that could adequately handle the extensive text of microbiology. Such text-based observations could not be reduced to a coded numerical equivalent in any simple way because, unlike a chemical

measurement, more than one answer could be required for any given field. Microbiology was not, however, somehow more general than chemistry, and attempts to reverse the direction of development ran into equal trouble. Because the logical differences often lay deep in the program design, and because these early programs were very rigid, unexpected limitations were difficult and expensive to overcome.

THE ROAD TO SOLUTIONS

The most compatible separate areas were chemistry and hematology, and early successful prototypes of general laboratory systems began by combining these areas. One of the first and most ambitious was the system designed by Berkeley Scientific Laboratories in the late 1960s and first introduced at the NIH Clinical Center and then at UC San Francisco. Abroad, Swedish and British developers were also at work.

As has often happened with medical computing, what were first presumed to be a simple set of engineering tasks were found to depend upon clinical decision making situations that had never been described in procedural terms. Consolidating data from separate laboratory sources into a single report led to the elusive search for the optimal reporting format--only to discover the obvious--that, given the multiple uses to which clinical data are put, all hard copy formats fall short in one manner or another. Not even the flexibility of electronic displays can resolve all such issues on a conventional terminal.

The hierarchical file structures of the 1960s were appropriate for patient oriented files, but the unpredictability of what test would be asked for and what data would be collected made fixed length record formats, such as those favored by ASSEMBLER, COBOL and FORTRAN, very inefficient unless additional pointer structures were introduced. The retrieval of data across patients for various administrative purposes, such as laboratory quality control and workload statistics, required separate pre-planned inverted files. Once again, the diversity of the activities in different laboratory sections made common conventions difficult. The sparse arrays and flexible field lengths of the Massachusetts General Hospital Utility Multi-Programming System or MUMPS offered the first convenient prototyping environment that could respond to the wide variety of ad hoc changes that were needed to explore the many sided and incompletely understood requirements of laboratory systems.

LOOKING BACK

From the perspective of 1977, Professor T. P. Whitehead summed up the evolution of the field at the Second International Conference on Computing in Clinical Laboratories in Birmingham, England, as follows:

Frequently there are four phases in the application of technological innovations in medicine. The over-optimistic introductory period lead by enthusiasts, a second phase of developing pessimism as the limitations and

full costs of the innovation are realized. The third phase is a recovery phase where the balancing of the claims of phases one and two are achieved, and finally the fourth phase where the innovation is applied at its correct level. [8]

Those who have studied the process of technological innovation as a general phenomenon of our time have found similar patterns representing discontinuous conceptual steps in many emerging technologies. Sahal and Foster [1,2] identify an initial turbulent phase--fraught with optimism, pessimism, diversity, and absurdity--followed by a coming together of understanding and design around a benchmark configuration that serves as a guidepost for successful future implementations. The cited authors present extensive analyses. Both emphasize the dynamic nature of technology so that no company involved in manufacturing and selling a product, faced with the flux of new demands and new ways of doing things, can afford to stand still. But to develop new products is to incur new uncertainties....

Luckily, in the formative 1970s in the United States, the clinical laboratory was a profitable revenue center, which coincided with the need for capital to explore new technologies and to pursue computer based information systems. There was, in effect, enough money to absorb the costs of development and accept the risks of failure.

These very real risks of the time were clearly presented by J. Lloyd Johnson and Associates in their 1975 study on "Achieving the Optimal Information System for the Laboratory". [9] In this study, a successful system was considered to be one that had some of the instruments in chemistry and hematology on-line, with any three of the following functions:

- o Test request entered through a videodisplay terminal or by some more efficient manner,
- o Collection list with labels printed,
- o Tests results entered without manual re-entry of patient or other specified number,
- o Ward report printed, and
- o Cumulative summaries printed.

Their extensive review concluded that 25% of hospital laboratory systems had achieved satisfactory working status for less than \$1000 per bed (recalculated in 1975 dollars and adjusted for hospital size), 25% required approximately double this amount and, no matter how much was expended in money and effort, one half of the hospitals could be expected to lose their entire investment! Looking backward, all strategies appeared risky, whether programmed in-house or supplied by vendors [10]. Success was felt to depend upon the tautologous wisdom of "understanding one's needs", plus certain analytic skills to be provided by experienced consultants.

THE TURNING POINT

Even as the Johnson study appeared, a turning point had been reached with the advent of the DEC based CLINLAB and the Hicks LCI systems. Limited in scope and rigid in language, these systems were the necessary benchmark examples that illustrated how separate functions could be brought together using tables and indirection to provide flexibility. One might well suggest 1973 as the year when the interaction between a computer team and a clinical laboratory began to have more than a 50:50 chance of success. As a consequence, the period from 1970 to 1980 became one of growth and ferment for vendors, for programmers, and for laboratories, but also one of confusion for hospital decision makers. No sooner had an effective system been identified, than a more effective one appeared to out-perform it. DEC based assembly language systems were overtaken by the FORTRAN systems of MEDLAB and Community Health Computing. Toward the end of the decade, these in turn were challenged by the MUMPS based systems of MEDITECH, Sunquest, and Medical Data Corporation. There were many other players, and the clinical reference laboratories followed a pathway of their own with BIOSCIENCES using IBM equipment and RUBICON using MUMPS. Each new wave took advantage of a language that supported more flexibility than its predecessor, and new hardware came along to make up for the lack of speed introduced by the added complexity. However, at a deeper level, a consolidation of understanding was taking place that focused on the formal modular nature of these systems and on the complex relationships that linked the flow of patient specimens and data through the laboratory to the clinical care givers and, secondarily, to the medical record and on to the billing office [11,12].

Some laboratory areas, such as blood bank, were so different that they were brought under a common framework later than others, and separate systems that serve this specific need remain viable today. But the attempt to automate the whole laboratory by a "mix and match" of computer systems from different vendors found the unified concerns of patient care a difficult task-master, and clinical demands mitigated against such fragmentation. The clinically satisfactory line of attack proved to one of synthesis and consolidation of specific functions into an ever more inclusive configuration that remained under the control of those that used the system.

By 1980 laboratory systems had converged on an interactive design that placed a terminal at every workstation or instrument interface, that consolidated patient data in a common database, that viewed intra-laboratory task organization and communication as the key design parameters, and that used differentiated subroutines to carry out the specific laboratory information tasks of each department [13]. This mature design recognized the unique perspective of each laboratory section, but managed to subsume these differences under a common framework that could take advantage of all of the major capabilities of computer systems: calculation, archiving, message transmission, and the support of workstations. Such systems have

now become the broad based backbone of effective laboratory operation.

Today, vendor product differentiation depends upon service support, price, and special features rather than fundamental differences in scope and performance [14]. In 1987, one can expect a successful implementation of a well tested system in better than 90% of the cases. Indeed, the functional requirements for most laboratory areas can now be stated with such self evident clarity [15], that it is hard to think back to a time when these specifications were difficult to formulate. They were indeed so, before the present ledge was reached.

THE NEXT LEDGE

On our present "ledge" we still have some cleaning up to do. There are new areas of laboratory responsibility; there is uploading and downloading to personal computers, and there is remote but secure access from physician offices. But the major task still to be completed lies in bringing together laboratory computer systems with all of the other clinical systems that support patient care (hospital information systems, pharmacy systems, and the like) into one consistent, patient oriented, organic whole. In this larger arena, we are today where we were in the laboratory ten years ago: we must introduce consistency without sacrificing the diversity that is characteristic of productive professional work patterns.

The historical experience of the clinical laboratory overwhelmingly supports the power and practicality of bringing together the different perspectives of different work environments under the common logic in a single system design, but it also points to the difficulty and subtlety of doing so.

However, as we peer up toward the next ledge, we will have to come to terms with the clinically derived knowledge bases and expert systems that loom ahead. To the extent that these new systems, now in their infancy, must rest upon real data acquired in real time, they will have to depend upon robust and fully consistent information systems that can generate the necessary clinical archives from which these relationships can be constructed.

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HEALTH CARE INFORMATION SYSTEMS

A Personal Historical Review

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INTRODUCTION

In 1961, a major career change occurred when I abruptly went from medical practice into medical computing. I had practiced internal medicine since 1942, had been Chief of Medicine in Kaiser Permanente's Oakland Medical Center, and I was Physician-in-Chief of Kaiser Permanente's San Francisco Medical Center when the Founder and first Executive Director of Kaiser Permanente, Dr. Sidney Garfield decided that it was time for the organization to begin to use computers in the practice of medicine. Since he knew that I had a degree in electrical engineering before I went to medical school, he told me that he felt I should get involved in medical computing and plan to use computers and technology to develop better methods for taking care of patients. In September 1961, Kaiser Permanente established a Department of Medical Methods Research.

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Reflecting back, our primary goal was to develop a comprehensive health care information system to provide an integrated, continuing patient medical record. Kaiser Permanente was an ideal environment for such an activity since it provided comprehensive medical care to patients, often continuing from cradle to grave, including ambulatory and hospital care, with all the ancillary and supporting services. Furthermore, Kaiser Permanente had multiple medical centers in the San Francisco Bay Area; and patients freely obtained care in Oakland where they lived, or in San Francisco where they worked. As a practicing physician within a group practice, the major problem was that the patient's medical record was not available for 10-15% of office visits since it would be enroute somewhere from a prior visit to another physician. To always have access to the patient's relevant prior medical information was of the highest priority. The essential information from every office visit, every hospitalization, every lab test and x-ray, every consultation and procedure always should be available whenever any physician needed it, wherever in the system the physician was located. Another common problem was that when the record was available, it often was so thick, containing

the accumulated documents over many years, that it was a time consuming chore to manually browse through the record to find the desired relevant past data. It would be a great blessing to physicians to exploit the power of the computer (with its communications) for storage, search and retrieval, and for the rapid transfer of patient data to multiple physicians in all facilities. To develop such a health care information system (HCIS) became the driving goal that directed our next 20 years.

In studying our group medical practice, it was found that 80 percent of physicians' services were for outpatient care and 20 percent for hospital care. Approximately one-fourth of all visits to the clinics were to the department of medicine; and more than one-third of all new patients requesting appointments with internists wanted a health checkup. In the hospital services, it was determined that about one-third of the daily hospital costs were for information processing (reporting test results, communicating orders, etc.). Accordingly, we concluded that we should direct computer applications to these areas.

MULTIPHASIC TESTING: A MINI-HCIS

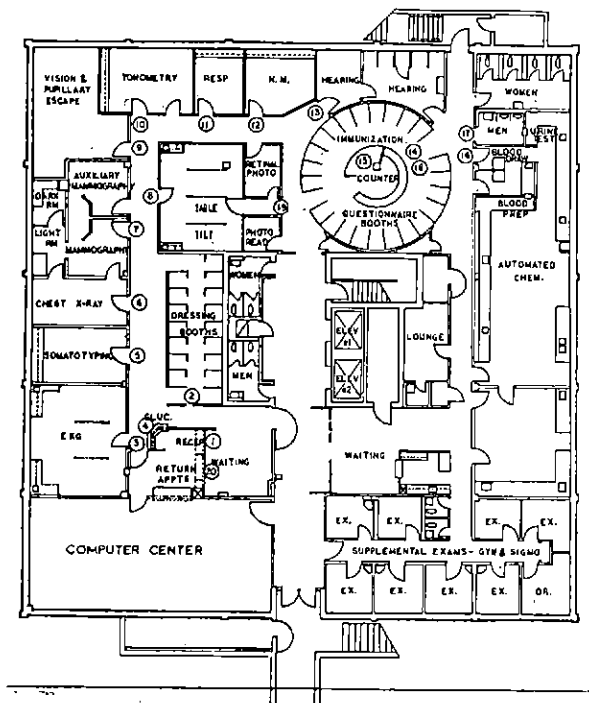
Since the beginning of our organization, Dr. Garfield had established preventive medicine as a basic service to be included as a prepaid benefit. Accordingly, the medical department was obligated by contract to provide health checkups to well persons within its budget, which had to be competitive with other health plans that only provided diagnostic checkups and sick care and did not include as covered benefits any health checkups or well care. As a result, in 1951, we

developed in the San Francisco and Oakland medical centers a lower cost, systemized programmed approach to providing health checkups based upon the experience of Dr. Lester Breslow who, as the San Jose Public Health Officer, modified mass screening by using a battery of low-cost screening tests, which he called multiphasic screening. The Oakland and San Francisco multiphasic screening systems solved the problem of containing costs, while they each processed 40-50 patients a day.

With the initiation of the Department of Medical Methods Research (MMR) in 1961, it became evident that the multiphasic screening program was an ideal system to use as a site for research and development in medical computing. Firstly, all the patients were relatively healthy, seriously ill patients never went through the system, if we made any mistakes in the system we probably wouldn't jeopardize anyone's health. Secondly, the multiphasic system was actually a mini-health care information system since it included patient's identification, appointment scheduling, registration and referrals, patient's histories, physician's physical examinations, diagnoses and follow-up referrals, lab tests, x-rays, ECGs, physiological measurements (blood pressure, spirometry, etc.), specialty procedures (tonometry, visual and hearing acuity), immunization records, and others. Finally, the developmental costs for such a mini-system's approach appeared to be manageable and should eventually pay for itself.

In 1962, we obtained our first of a series of grants from the USPHS to automate and improve our existing manual multiphasic screening

During the late 1970s, Oakland patients went through 20 stations in 2-3 hours. When a patient made an appointment for a multiphasic examination, a packet of data processing cards, onto which results from tests would be punched or marksensed, were prepared by prepunching into the card the patient's medical record number. Patients registered approximately one every three minutes. They each received a clipboard containing a check-list medical history questionnaire form and a packet of cards



The self-administered check-list medical questionnaire form, which the patient received on registering, had been completed during any waiting periods between stations. The patient was then assigned to a questionnaire booth and received a letter box containing a deck of 207

prepunched cards, each having a single dichotomous question printed on the card. (Figure 2) Typical "inventory by systems" questions had been selected that were judged to be medically of value in discriminating patients with specific diseases from those nondiseased. The patient responded to each question by taking the card from the top section of the divided letter box and dropping the card into the middle section if his answer to the question is "yes," or into the bottom section if his answer is "no." This procedure automatically sorted "yes" responses for direct input to the computer by means of a card-reading machine. In order to test-retest the "yes" responses, when the patient had completed sorting all the questions, the nurse removed the "yes" cards from the middle section of the box, placed them back in the upper section and asked the patient to go through them once more "to be sure the answers were yes." This

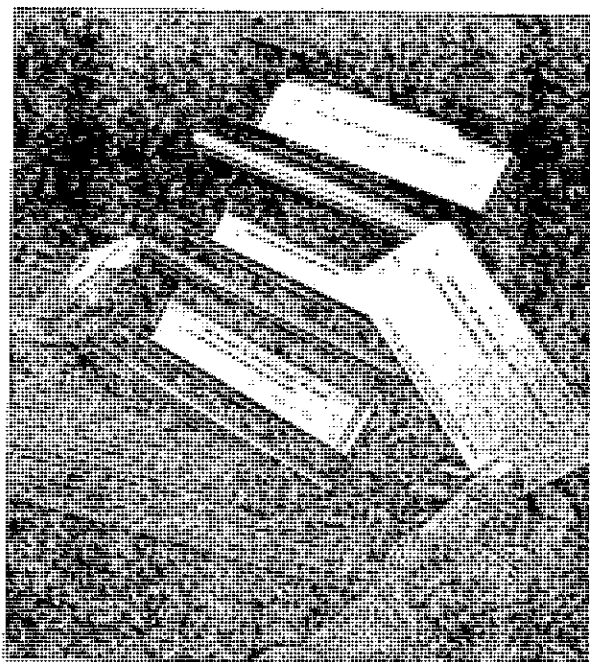


Fig. 2. Sorting prepunched health questionnaire cards

additional step decreased the "false" yes responses by about ten percent.

The patient was then sent to the laboratory where blood samples were drawn for a hemoglobin test, white blood cell count, venereal disease research laboratories test for syphilis (VDRL). The test values were recorded on marksense cards. From a single sample of serum, eight blood chemistry determinations (serum glucose, creatinine, albumin, total protein, cholesterol, uric acid, calcium, and transaminase) were simultaneously done within twelve minutes by the first multi-channel automated chemical analyzer made by Technicon. We interfaced a cardpunch machine to the chemical analyzer so test results were directly punched into cards. (Figure 3)

A urine specimen was collected, and tests were done for pH, blood, glucose, and protein (paper strip tests). The results were entered on the patient's test marksense card.

The patient returned to the questionnaire booth and then received a second box of questionnaire cards for psychological testing. The patient sorted 155 psychological questions into "true" and "false" responses, using the sort

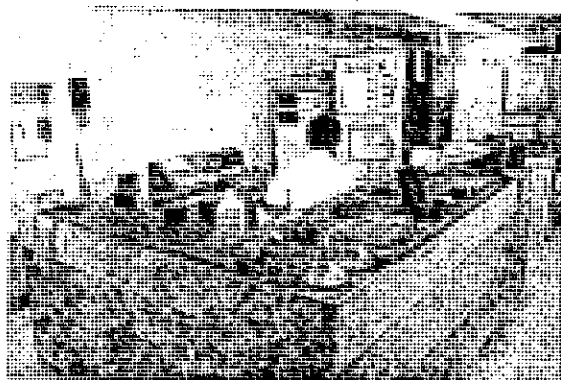


Fig. 3. First eight-channel Auto Analyzer interfaced to automated card punch

box in the same manner as with the medical questionnaire.

By the time the patient had completed the psychological questionnaire, the "on-line" computer processing had been completed, and supplemental tests and appointments, "advised" by the programmed rules of the computer, were arranged for the patient. Routinely advised were a sigmoidoscopy for all patients aged 40 or more; and, for women, a gynecologic examination with cervical smear for cancer detection.

Most of the data generated in the automated multiphasic laboratory were recorded on prepunched or marksense cards to permit their immediate introduction into the data processing system. As an "on-line" procedure, while the patient was in the last station, the computer processed the information from the punched cards from anthropometry and chemistry; the prepunched sorted cards from the medical questionnaire box; and the reproduced marksense cards from spirometry, hearing, vision, urine tests, hemoglobin determination, and white cell count. The punched cards were read into a data communication system, and the data transmitted via telephone line to the central computer in a separate building in Oakland.

The computer processor went through a program routine containing various test limits and decision rules, and printed out a report constituting "advice" as to any additional procedures that should be done before the next visit and the time and length of the follow-up appointment with the physician. For example, if the urine analysis showed proteinuria, the computer printed out instructions to the

receptionist to ask the patient to return to the laboratory with a first morning specimen for re-test. If a serious abnormality was detected, the computer printout advised the receptionist to arrange an early appointment with the physician; and in some instances to ask the nurse to take the patient to see a physician in the emergency room.

The efficiency and quality of the multiphasic testing process was the result of the standardization of the repetitive procedures routinely included in health checkups, in contrast to the variability of sick patient examinations. At the last station, where a physician had previously manually reviewed all test results and then arranged for any indicated secondary tests, or re-tests of abnormalities found, the computer's automated review and advice rules now replaced this reviewing physician.

As an off-line procedure, the computer collected and stored the remaining information which arrived a few days later (marksense cards with physician interpretations from the ECG and x-rays, the remaining laboratory test reports, and the key-punched medical questionnaire form). When all information had been received and stored, the computer produced a printed summary of all test reports and history questions answered "yes." (Figure 4)

At the time of the patient's first office visit, the physician reviewed the summary report and directed further history review toward elaborating the questions to which the patient has answered "yes," and to the test abnormalities reported from the automated multiphasic laboratory. The physician completed a physical

examination, recorded the findings and diagnoses on a preprinted form, which was automatically scanned by an optical mark reader, and then arranged whatever medical care was necessary for the patient in the usual way.

Our clinical decision support program at that time consisted of two sequential processes: (1) decision rules to provide "advice" on secondary sequential testing, and (2) likelihood ratio probabilistic programs to suggest that the physician "consider" likely diagnosis. Consider rules were developed for a variety of diseases (bronchial asthma, gastrointestinal diseases, heart disease, diabetes). The neuromental

questionnaire, the basis for developing consider rules for psychiatric diagnoses, was given to 10,000 patients in 1966 and 4% received "consider refer to psychiatry" for conditions which made up 85% of psychiatrists' diagnoses. This work was discontinued after one year, and never published as our psychiatrists were concerned it might not be appropriately used by internists and might overload the psychiatrists' schedules.

The statistical approach used by this "consider" program was the method published in 1950 by Neyman. The data necessary for this method were the determinations for each disease of the proportions of individuals with the disease who had certain selected sets of symptoms (or tests), and the proportions of individuals without this disease who had the identical sets of symptoms (or tests). On the basis of a patient's response to questions (and tests) directed toward eliciting these specific symptoms, the individual was placed into one of two categories: either he warranted further testing since he was likely to have the disease, or he did not warrant further testing for the disease. The degree of likelihood of the patient falling into the disease category was determined by criteria previously established and varied according to the disease under consideration. Thus, Neyman's method was based upon selecting sets of symptoms whose relative frequency in diseased and nondiseased patients established likelihood ratios which were used to define a region having the maximum likelihood of detecting the disease if present, and at the same time, a predetermined likelihood of falsely detecting the disease. The frequency was determined of the

PERMANENTE MEDICAL GROUP - OAKLAND
FINKL SUMMARY REPORT - MULTIPHASIC HEALTH CHECKUP - 2/24/65

DOE, JANE
M.R.NO. 9876543 BIRTHDATE 05-27 FEMALE U.A. SMITH J J
OAKL.

ANTHROPOMETRY: 127.5 LB., 64.5 IN

ECG: LT. VENT. HYPERTROPHY
PHONOCARDI: SYSTOLIC BASAL MURMUR
SUPINE BLOOD PRESSURE: 165/80 SUPINE BRACHIAL PULSE: 76.

VITAL CAPACITY: 2.3 L 1 SEC 3.2 L TOTAL
CHEST XRAY: CARDIAC ENLARGEMENT HEART/CHEST RATIO .52
BREAST XRAY: NSA

VISUAL ACUITY: R.E. 20/40 OR BETTER L.E. 20/40 OR BETTER
PUPILLARY ESCAPE: NO PUPILLARY ESCAPE L.E. NORMAL
OCULAR TENSION: R.E. NORMAL L.E. NORMAL
ULTIMATE PHOTO: MINIMAL DIABETIC RETINOPATHY
HEARING: NO CLINICALLY SIGNIF. HEARING DEFECT

URINE: PH & GLUCOSE NEG. PROTEIN 0 BLOOD U BACILLI NEG.
CLINITEST 1+2 ACETONE 0
URIC 0 BLOOD GROUP AB LATEX AGGLUT. 0
HEMOGLOBIN 12.3 GM (NORM. 12.0-15.2) WHITE COUNT 9,000

SERUM: (NORMAL)
GLUCOSE (1 HR.) 215 MG (UNDER 200)
GLUCOSE (12 HR.) 170 MG (UNDER 150)
TOTAL PROT. 6.7 GM (5.8-7.8)
ALBUMIN 4.0 GM (3.4-5.0)
CREATININE .90 MG (UNDER 1.3)
2 HR. BLOOD SUGAR 10 MIN. LATE

SERUM: (NORMAL)
CHOLESTEROL 195 MG (140-270)
CALCIUM 9.5 MG (8.4-10.8)
URIC ACID 3.9 MG (3.0-8.3)
SGOT 21 U (UNDER 50)

PATIENT RECEIVED THE FOLLOWING (ADVICE RULE) DIRECTIONS:
700-2 HR. BLOOD SUGAR 800-ROUTINE MEDICAL APPOINTMENT

CONSIDER REFER TO ASYMPT. DIABETES STUDY IF FOLLOW-UP CONFIRMS DIABETES.

PATIENT ANSWERED YES TO THESE QUESTIONS ON 1964 FORM:
244-HAD BAD REACTION OR SENSITIVITY TO PENICILLIN?
IN THE PAST MONTH?
434-THROAT BEEN SORE ALMOST EVERY DAY?
IN THE PAST 6 MONTHS?
450-SHORTNESS OF BREATH WITH USUAL WORK OR ACTIVITY?
IN THE PAST YEAR?
470-REPEAT PAIN, PRESSURE, TIGHT FEELING IN CHEST IN MIDDLE OF BREAST BONE?
478-REPEAT PAIN, PRESSURE, TIGHT FEELING IN CHEST WHEN SITTING STILL?
482-REPEAT PAIN OR PRESSURE, IN CHEST WHEN WALK FAST, LEFT ON REST?
483-REPEAT PAIN, PRESSURE OR TIGHT FEELING IN CHEST WHEN STOP WALKING?
484-REPEAT PAIN OR PRESSURE, IN CHEST LASTING MORE THAN 10 MINUTES?
574-ALWAYS HAVE TO GET UP FROM SLEEP TO URINATE?

CONSIDER ABNORMAL, OR POSSIBLE VARIATION FROM NORMAL
NSA=NO SIGNIFICANT ABNORMALITY
* NOTE

Fig. 4. Example of computer printout of summary report

combinations of symptoms which actually occurred in a group of patients with the specific disease and in another comparable group of persons without this disease. The ratio of the frequency of the set of selected symptoms in the diseased patients to the frequency of this same set of symptoms in the nondiseased was termed the likelihood ratio. The ratios were then arranged in order of increasing magnitude. The region for which a "positive" diagnosis was made (termed the "positive region") was then demarcated by selecting a specific ratio from a consideration of the sensitivity and specificity of this test. All symptom sets associated with ratio values equal to or higher than the selected ratio were included in this positive region. Those symptom sets with ratio values less than the selected value fell outside this positive region, and were therefore in the region for diagnosing the nondiseased (termed the "negative region"). We preferred the likelihood ratio method to other probabilistic methods (such as Bayes theorem) because it did not require symptoms to be mutually exclusive, we did not need to know disease prevalence in our patients, and clinicians seemed to understand it easier.

Our experience with the multiphasic health checkup showed that computer data processing with a continuing, integrated patient record file provided to the physician in a timely manner, a comprehensive profile of the patient's current and prior status. It allowed efficient handling of large volumes of medical information on greater numbers of patients over long periods of time. It permitted test and data online quality control, thereby decreasing rates of errors due

to instrumental variations, personnel errors, and insertion of data into wrong patients' records.

The productivity of physicians was greatly improved when they completed health checkups to patients who had received prior testing by automated multiphasic laboratories. Where automated multiphasic testing had been completed in advance of the physician's physical examination, 50 to 70 percent of patients completed their "checkup" with one visit to the physician. With the addition of computer "advice" rules which automatically proposed necessary retesting and additional procedures, 90 percent of patients could be taken care of by one physician office visit.

Multiphasic health testing provided not only more information on more patients, but more information on each patient, thereby producing greater individualization of patient care. Broad and less appropriate population norms were not used since the computer permitted application of specific norms to each individual patient, based upon age, sex, height and weight, time of day, and hours since last food ingestion; thus improving the quality of testing. Since the boundaries between health care and sick care were primarily controlled by programmable limits for normal vs borderline vs diseased, this capability to generate specific normal values was essential to minimize the numbers of false positives and false negatives. With all patients required to be seen by their physicians following the multiphasic laboratory testing, the problems of handling false negatives and positives were then similar to those for periodic health examinations by any traditional method. With the great

concern about misleading results from unordered routine procedures, computerized quality control reminded physicians that the traditionally collected information in the patient's medical history and physical examination also had a substantial error rate.

Automated multiphasic health testing rapidly diffused during the late 1960s so that in the early 1970s there were a few hundred programs in the United States, several in Europe and in Japan. We had so many visitors to our Oakland multiphasic center in the late 1960s that the USPHS gave us a contract to support a half-time physician to conduct tours. The Japanese drove up in buses and took pictures of every phase of the Oakland multiphasic center, and then duplicated it in Japan. Congressman Fogarty paid a special visit to the center and was very impressed when the computer printed out while he was standing there to consider leukemia in a patient. The next day, he called from Washington to ask if the diagnosis was correct, and indeed it was. However, since the costs of providing health checkups to well persons was not paid for by health insurers, multiphasic programs gradually closed down in the United States except in health maintenance organizations (HMOs) which included health checkups as a prepaid benefit. In Japan, in France, and in some other European countries, automated multiphasic programs still continue to operate.

Automated multiphasic testing provided a useful experience for us in developing a computer-based mini-HCIS; and demonstrated how essential was stable financing for the continuing development of a large technological system.

From the viewpoint of providing us with experience to go forward in developing a HCIS, the multiphasic system had required development of computer processing of:

(1) Patient identification data, appointment scheduling, daily patient appointment lists, preparation of card packets, specimen labels, registration, operations control data, statistical reports, and quality control procedures.

(2) Patient data including patient history, physicians' physical examination data, test and procedure results, physician interpretations of ECGs and x-ray diagnoses.

(3) Clinical decision support including alert and warning signals for findings outside of predetermined normal limits, "advice" rules for secondary sequential testing, "consider" rules for likely diagnoses; comparison of history questions with previous histories and signal "new" symptoms reported by the patient for the first time.

(4) Provide research data services for epidemiological, clinical and health services research.

(5) Provide a continuing, long-term patient computer medical record to permit comparisons of current patient data to prior data for clinically significant changes.

(6) Provide a system with reliability, security and confidentiality.

The computer file strategy which evolved an integrated, continuing variable length, variable format will be described in the next section.

PILOT HCIS

In 1969, we received a grant from the newly established National Center for Health Services Research and Development (NCHSR&D), and its first Director Paul Sanazaro. We were one of seven Health Services Research Centers (HSRC) and ours had its focus in medical technology and computer applications. The objective of our HSRC was to develop a computerized medical data system using San Francisco as a pilot hospital. Ted Van Brunt was the project chief of the San Francisco hospital computer system and Lou Davis was manager of the computer center containing two IBM 360/50 computers (Figure 5) and was responsible for developing the computer-stored medical record and its data base management system.

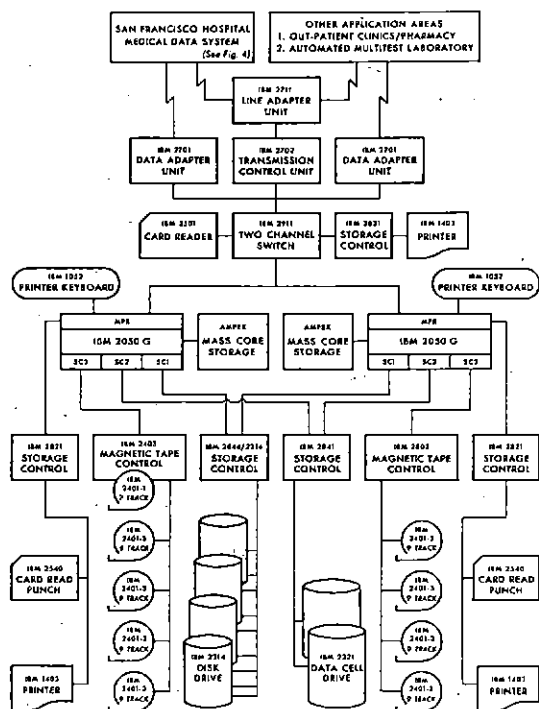


Fig. 5. Equipment configuration for computer center in 1970

By 1973, in our San Francisco Permanente Medical Group offices, patient registration data and physicians' diagnoses from 13 outpatient clinics for 2,000 visits daily were recorded on specially designed, standardized "encounter" forms. Between 90 and 95 percent of the diagnoses were entered by the physicians from a structured format. The remaining unstructured data were manually inscribed on the form and required keypunching for input. The data from these forms were initially entered by optically scanned forms, but later the data were entered by on-line electric typewriters directly into each patient's computer record.

In the outpatient pharmacy, the data from 1,200 prescriptions daily (including patient and physician identification, drug name and dose, prescription refill and drug usage data) were entered by pharmacists using online electric typewriters connected by telephone line to the central computer, directly into the appropriate patients' computer medical records. These records resided in direct-access mode in the central computer facility. Subsequently, upon entering the prescription refill number, a new label was printed and the cumulative number of dispensed prescriptions automatically recorded. Container labels were produced under program control, to be dispensed with the drug. We had also reviewed a contract from the Food and Drug Administration to use the San Francisco drug and diagnoses data to develop a drug reaction monitoring system.

A clinical laboratory computer system was operational which could handle data for 3000 tests a day. The automated multiphasic health

testing program in San Francisco, described above, entered the data for 150 patient health checkups a day. An online electric typewriter in the emergency clinic could retrieve at any time selected or all of the above outpatient data from the patients' computer medical record. (Figure 6)

By 1973, the pilot HCIS was being tested within our San Francisco Kaiser Hospital on the Pediatric Service and with a general admission-discharge-bed census application. The hospital data subsystem consisted of a satellite mini-computer linked by telephone line with the central computer facility in Oakland. The satellite processor drove 24 visual display terminals, each with associated "light-pen" sensor, and an electronic printer enclosed in a sound-proofing box. The physicians identified by plastic identification cards, were able to enter orders and patient's diagnoses directly into the computer by using a light pen. Nurses, using

their plastic identification cards, could similarly chart administered drugs to inpatients.

The system of terminals was evaluated by Pediatric doctors and nurses for data input and output of diagnoses, physicians' orders (including orders for drugs and general nursing orders), drug administration data, medication schedules, and clinical laboratory results.

A computer-stored, continuing, integrated medical record was operational which was so structured as to store all classes of patient-related data: identification, administrative, and medical, inpatient, outpatient, and ancillary records. It was capable of continual updating over the lifetime of the patient, of accepting the variable format of medical data input, and of responding to the need for real-time inquiry to individual patient records. All records were individually retrievable by each patient's medical record number on a direct access basis. Each individual's record within the computer

direct access storage facility was kept and moved together as a continuous string of data; it was never split or fractionated for any reason.

The primary file for the medical record data base consisted of 1.2 billion bytes of on-line direct-access disk storage. A patient computer medical record (PCMR) existed for each patient in the Health Plan. Each PCMR formed a physically contiguous record in the file. When a PCMR was updated with new medical data, the entire PCMR was rewritten on disk, with the new data inserted in its proper place. This file then contained all medical data and current essential identification and administrative data. Non-essential or obsolete identification and

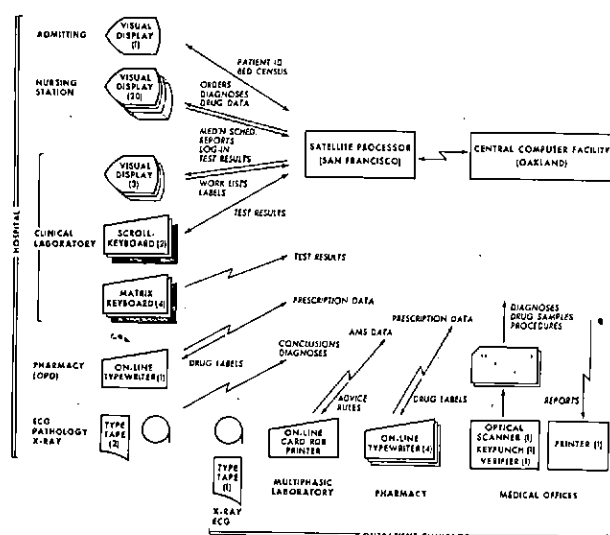


Fig. 6. San Francisco pilot HCIS in 1972

administrative data, which were not needed for real-time applications, were stored on magnetic tape and constituted an off-line data base in a lower hierarchy than the on-line file. The data base resided on 12 IBM 3330 disk drives, each of which had a storage capacity of 100 million bytes. The effective maximum capacity of this file was about 1.2 billion bytes. Of 1.5 million PCMR's in the data base in 1972, about 1.0 million contained only identification and administrative data. Of the remaining 500,000 records, the average PCMR had an average length of 1,600 bytes and contained seven visits.

The PCMR was a logical branching tree structure in which information was represented at each branch point (node) by data elements, and in the hierarchical structure by the relationship between nodal points (Figure 7). Data was stored at the nodes in two different forms: fixed-length, fixed-format indices and variable-length, variable-format definitions and values. Relational data between nodes was implicitly

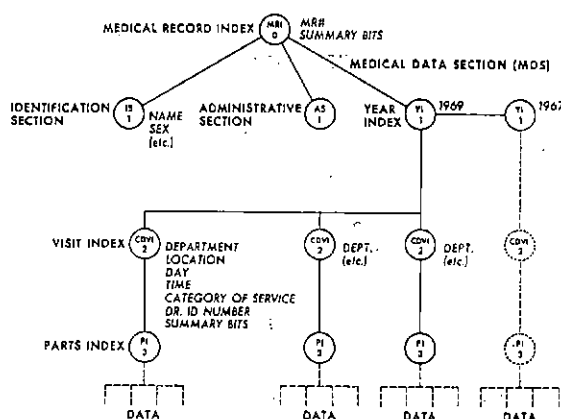


Fig. 7. Tree structure for computer medical record

represented by the tree structure itself: data elements within a node or subtree modified the higher level nodes from which they branch. There could be as many as 13 node levels in a PCMR. Indices, which were of fixed length and format, served primarily as pointers to specific portions of the PCMR. They also contained certain types of identification and visit data. The medical record index at level 0 contained the patient's seven-digit medical record number, summary bits, various counters and field lengths. The year index at level 1 was in the Medical Data Section, and contained the year of visit or visits. A computer defined visit index at level 2 was in the Medical Data Section, and contained visit parameters and dates. The parts index at level 3 specified the parts into which medical data from a visit had been stored.

Summary bits were a series of 56 binary flags that were set whenever certain data are stored. There were bits corresponding to general and specific data categories, procedures, and laboratory specimens. The principal function of summary bits was that they were easily and rapidly tested by retrieval programs to determine whether the data of interest were present in that record.

Within a PCMR, data was stored in one of three main sections: identification, administrative, or medical. The Identification Section contained all secondary identifiers and other information characteristic of the individual patient. The Administrative Section contained information on Health Plan coverage, Medicare, and other data of a nonmedical nature. The Medical Data Section contained medical data

Table 1. ESTIMATED HCIS 1973 COSTS

<u>COMPUTER CENTER</u>	<u>ANNUAL COST</u>	<u>UNIT COST</u>
Staff and Equipment	\$1,000,000	\$1.00 per member/year 0.18 per office visit 1.50 per hospital day
Computer Medical Record	250,000	0.25 per member per year 0.09 per office visit 0.25 per hospital day
<u>APPLICATION</u>		
Multiphasic Testing	50,000	2.50 per patient
Clinical Laboratory	50,000	0.06 per test
Pharmacy	15,000	0.05 per prescription

for each patient visit, indexed and stored in reverse chronological order. Medical data was further subdivided for storage purposes into 10 parts. Each part represented a general category of medical data. History data was stored in Part 0, laboratory data in Part 2, physician reports on x-rays, ECGs, etc., in Part 3, nurses notes in Part 4, diagnoses in Parts 5 and 6, prognoses in Part 7, treatments in Part 8, other recommendations in Part 9. Within each part, data was stored in a tree structure.

The pilot HCIS described above was developed and tested, and financially supported about half from federal research funds and about half from our organization. The research support funds were discontinued in 1973 with the termination of the Health Services Research Center grants. As a result of the large capital cost requirements, associated with the development of the HCIS, an organizational decision was made to discontinue this program.

By the end of 1973, there had been sufficient experience with testing and operating the HCIS so that its costs were identifiable. Table 1 lists the estimated costs for staff, services, computing equipment and data base

storage for the Oakland and San Francisco regional medical services computer operations.

We were reminded that Galbraith had pointed out the extraordinary requirements of large complex technological systems, which needed long-term, heavy investment of capital equipment and manpower, accurate planning to inflexibly commit people and capital for long lead times, specialized technology manpower, and a long-term commitment from an organization competent to coordinate mixed medical, systems, and engineering specialists.

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The Perception of System and the Reduction of Uncertainty

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Summary

Until the mid 1960's we had two separate streams of development of medical information systems. One proceeded from efforts under the Hill-Burton Program to develop management systems for hospitals and community health planning, with little stress placed initially on the interactive use of computers. The other, centered within medicine, and medical decision making, was from the outset an effort to exploit the growing potential of computers in clinical matters. Creation of the National Center for Health Services Research in 1968, was a key event in the merging of these two sets of activities, with formation of a program and study section in health systems development and a common source of funding for projects with either administrative or clinical significance, or both.

The establishment of the National Center was preceded by more than a decade of health services research with the objective of improved management systems. The concepts and systems growing out of this research were forerunners of many of the activities in modern medical informatics; they were foundations for the still developing techniques of resource allocation, staffing, scheduling, and for screening and diagnosis.

A common theme runs through the early research and development. As a researcher one was faced with perplexing pictures of the behavior of both patients and the people and organizations serving them. Through direct observation of the central actions in patient care and support ser-

vices, it was possible to perceive some pattern, order, or system in the demands stemming from illness and accident, and these patterns were inherently variable and apparently unpredictable. Whether physician, nurse or administrator, the provider was confronted with the need to make decisions under uncertainty.

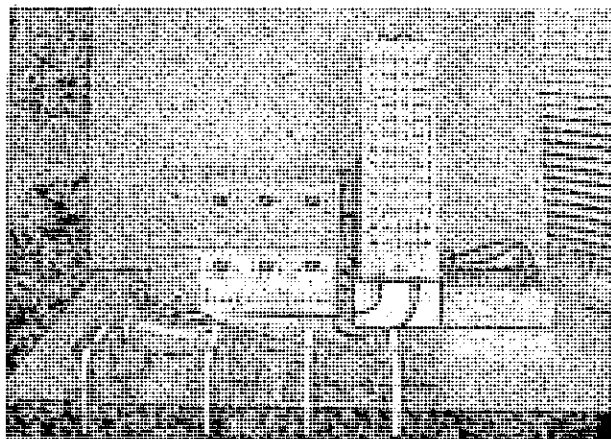
Having gained insight from research, the task was then one of finding ways to reduce uncertainty: by developing timely predictors of demands, by developing flexible administrative mechanisms to move resources to demands (or vice versa) and by reducing error in the assessment of patient condition. The early work in patient classification by level of dependency led to management systems for nurse staffing and patient placement. Refined by the inclusion of diagnosis as a variable patient classification led to mechanisms of resource allocation and reimbursement. In study of outpatient services, early work drew upon techniques of computer simulation to test alternative approaches to control of congestion and delay in outpatient services through computerized appointment scheduling, and records keeping systems. In applying statistical decision theory to disease screening early work led to awareness of the need to reduce uncertainty of testing, touching off a wave of efforts to base decision rules on multivariate analysis to increase sensitivity and specificity. The path to implementation of all these systems has led appropriately to computer based information systems.

In retrospect, one can see in the decades of research and development a process of inexorable growth of intelligence in an evolving health system, growth in precision of sensing, analysis, communication and memory. In this perspective, the disparate research and development efforts begun years ago find meaning in the context of medical informatics, and the role of medical informatics itself can be better understood in the context of the evolving health system.

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Introduction

Inspired by the 1963 photograph of Drs. Clark and Molnar with the LINC, I recalled my own efforts along somewhat similar lines and dug from the files a picture of the QUEUIAC. While working with Paul Dunn in the Intelligence Division of the Army Operations Research Office in the early 1950's, we built a device to simulate the random flow and congestion of battlefield communications and to demonstrate the effect of changes in technologies, message handling, and decision processes (Dunn et al., 1956). The QUEUIAC, as we dubbed it facetiously, was a simple machine - banks of bi-directional stepping switches actuated by variable speed paper tape drives. Tapes were punched at intervals to simulate message arrival patterns and service times. It displayed the erratic pattern of system states - the number of messages in process or waiting - by rows of lights and was easily manipulated to show the effects of changed speed of transmission, priorities, or network configurations.



Typical QUEUIAC setup.

As a means of simulating real or hypothetical situations, the QUEUIAC had some good points. There was realism in its display of congestion and delay in operating systems subject to random demands. However, it was noisy and too slow for analytical work, i.e. the estimation of distributions of state probabilities and elapsed times to information processing. Rapidly developing techniques of Monte Carlo simulation using digital computers doomed the QUEUIAC to oblivion, but not before it - and awareness of the kinds of problems it addressed - caught the attention of people in the health services, and set in motion a set of activities and relationships that continue to this day.

One outgrowth of military operations research of World War II was a sharpening recognition of the pervasiveness of random processes and their consequences in human

affairs. Not only communication systems, but transportation, manufacturing operations, emergency care arrivals at hospitals - all were recognized as stochastic or chance dominated - processes requiring surplus capacity to accommodate uncontrollable peaks and valley of demands. While the mathematics of design of telephone systems had been worked out in the early part of the century, the formulas did not cover the range of waiting line problems (or queuing problems or stochastic systems) encountered in other fields. This gave rise to a number of efforts to solve particular type of problems analytically, but complications in real life systems quickly outran the capability for mathematical solution, hence the recourse to simulation.

Paradoxically, mathematical analysis is possible when the flow of messages, people, or other things is either tightly scheduled or when it is a completely unscheduled set of chance events. There is system - in the sense of patterns - in what might seem to be pure chance. It is the ability to perceive the obscured system in the pattern of random events that paves the way for designing appropriate human organizations to deal with those events. Whoever must respond to random events as they occur lives in a world of uncertainty, an unenviable position, particularly if resources are scarce. The natural tendency is to try to get hold of processes and to control the flow of events over time; to reduce the uncertainty of what is happening or what will happen next.

At about the time of these activities, the deans and administrators at Johns Hopkins met at the behest of the University's President, Dr. Lowell Reed, to determine ways in which the diverse schools and affiliated research agencies (which included the Army Operations Research Office) might give each other assistance. Thanks to the insightfulness of the Director of the Hospital, Dr. Russell Nelson; the Director of the Operations Research Office, Dr. Ellis Johnson, and my mentor, Dean Robert Roy, of the School of Engineering, the potentials of operations research approaches to help the Hospital were seen to be promising. The concept was given a try, beginning in 1956, with the establishment of an operations research division within the Hospital and it was my good fortune to head the group.

Early Operations Research in Hospitals-Inpatient Care

Once on the job some pressing problems were given priority. Recall that we are speaking of a period not long past World War II. The nation's building and renovation of health facilities was just beginning. Some floors of the hospital

were closed for lack of professional nursing staff. Substitutes in the form of nursing aides trained on the job helped to staff the open floors but understaffing remained a problem and work stress caused high turnover. There was urgent need for a system of equitable staffing assignments. In addition to the problems on the nursing units there was a great deal of congestion in the outpatient clinics. These conditions were recognized as symptoms of deeper problems in the totality of health services of the times but we could not wait for their solution at a national or community level. It was necessary to carry on through best use of the resources at hand.

One clue to the possibility of solutions lay in the observable fact that, while indeed there were periods of extreme congestion, there were also periods when not much was happening. In part this was predictably periodic, but in part it was sporadic and unexpected. Some work studies had noted considerable staff idleness even though there were complaints of personnel shortage. Administrators were quick to attribute this to poor supervision and it was around this point that some of our first studies were organized. The situation looked suspiciously like the natural consequences of inherently random processes affecting the levels of illness of patients as well as the availability of nurses. We set out to determine what we labelled an "optimum" staff and facility for a nursing unit and found that the optimum was something that varied continuously, but could be predicted and achieved. After painstaking hours of observation of patient care, there emerged first some evidence of different categories of patients, measured in terms of amounts of nursing care given. Patient dependency classification was not a new idea, but this work added knowledge about the day to day variation in numbers of patients in the categories or levels of dependency.

Of particular interest was the distribution of critical, or intensive care, patients, which closely approximated a Poisson distribution, evidence of the purely random process described earlier. This was not surprising, since the arrival, or relapse of intensive care patients into a tertiary care hospital was indeed an independent, random process and their length of stay was also highly variable (Flagle, 1960). The number of intensive care patients on the 30 bed wards varied from as few as 2 to as many as 15, and, since these patients received nearly five times as much attention as other patients, their number dominated the need for nurse staffing.

What made the problem tractable was that the patient classification could be made quickly on the basis of factors

observable to nurses, and that the work loads estimated were reasonable predictions for the following day. This work was reported by Connor, et al., (1961), describing how the process of patient dependency classification formed the basis of a management process for day to day computation of staffing requirements for inpatient nursing units in acute care hospitals. The information system developed for the management process was a manual one requiring daily patient classification by a head nurse, followed by a few calculations to arrive at predicted staff needs for the following day. It was the forerunner of computerized systems for nurse staffing (Miller, et al., 1975). Several such systems are marketed commercially today.

Several parallel developments took place, ultimately of significance to medical informatics - a term not even dreamed of at the time. While we at Johns Hopkins were concentrating our attention on day to day management of inpatient care by augmentation of staff in response to signals of predicted heavy workloads, colleagues in the U.S. Public Health Service were examining an alternative form of organization known as Progressive Patient Care (Haldeman and Abdellah, 1959). Like the Hopkins procedure, they recognized levels of intensity of care, but used patient classification as a basis for transfer to facilities appropriate to the level of need. Designed as a response to shortages of acute beds and special duty nurses, the concept of progressive care spawned the reality of the intensive care unit and the dream of hospital based long term care. The intensive care unit, by concentrating the number of critically ill patients gave economic justification and operational necessity to the automation of monitoring processes, a major area of importance for medical informatics.

Another development of importance emerged from the work studies and activity analysis of inpatient care. Though everyone knew that written communication consumed much of the professional nurse's time, the measurements came as a surprise - something on the order of a third of available nurse time spent in transcribing and other paperwork. The Lockheed Company can be credited with bringing aerospace technology to bear on this problem. Using light pen technology to activate a hierarchy of displays on a CRT, physician orders for medications and treatments, and nursing orders for procedures could be entered, analyzed, consolidated, and recorded for retrieval. My involvement was peripheral and not in the development phase. However, in 1968, while serving as Special Assistant to the Surgeon General, for applied health technology I participated in the economic analysis of the concept of the ward based hospital information systems, concluding that the commercial

potential was sufficiently large to justify industrial investment in its development, but that federal support of demonstration and evaluation would be an appropriate government role. Evaluation of the El Camino Hospital installation, supported by the National Center for Health Services Research, has provided quantitative information on a major product in the armamentarium of medical informatics (Coffey, 1980).

Another major development in research on inpatient care was related again to the notion of patient classification. Colleagues at Yale, John Thompson and Robert Fetter, examined patient classification from the point of view of overall resource requirements for an episode of hospitalization. Using data from hospital discharge abstracts, applying a computerized procedure for pattern recognition, Autogrp, they looked for clusters of patients with similar patterns of costs in terms of length of stay and use of other resources. Their groupings were strongly associated with diagnosis, hence the name Diagnosis Related Groups (DRG's) (Fetter, et al., 1980). This scheme of classification, not of the patient day but of the patient episode of hospitalization, has been adopted as a basis for hospital reimbursement of federally supported inpatient care. Within DRG's variation in length of stay is large; further refinements continue.

Studies of Outpatient Care

The problems of outpatient services, characteristic of large medical centers, were manifest in crowding and patient delays. Traditionally, if an appointment system existed, a large number of patients would be scheduled in early to avoid the possibility of physicians waiting for patients. Bailey (1952) studied the problem in England, reaching the conclusion that the phenomenon of patient delay, could be understood only if the ratio of imputed value of physician time to patient time was nearly infinite. Patients responded by disregarding appointment times or failing to appear; in a pediatric clinic studied it was not uncommon to have a missed appointment rate near 50%. The net result was a pattern of actual patient arrivals showing a high degree of randomness. The problem was compounded by a form of sequential and separate services, e.g., registration, payment, weighing in, interview, treatment and rescheduling of a subsequent visit. Variability in service times caused delays and congestion before each of these services. The situation lent itself to analysis by simulation, which proved to be a useful approach (Gabrielson, et al., 1962), for it permitted demonstration of the probable behavior of reorganized services. In the specific example of the pediatric clinic, simulation of parallel lines of patient flow relieved bottlenecks but pointed up

the need for tighter scheduling of patients and clinic staff. Manual systems were devised for this at the time, paving the way for computer based systems, still a few years away.

Both the inpatient and outpatient problems and the approaches to their solution had common characteristics. First was the need to perceive in the behavior of perplexing set of activities the dynamics of the demands of illness and accident on a system of health service resources. When it was seen in a quantitative sense that the dynamics of demand were largely dominated by chance, the way was paved for operational solutions. One approach was to combine operating units to take advantage of the relative reduction of chance variations as size increases. This was illustrated in a simulation of the effect of combining maternity units (Thompson et al., 1964). Another was to develop means of predicting future demands in time to deploy resources, as in the case of the inpatient nurse staffing. A third was to regulate the flow of scheduled patients to compensate for the uncontrollable, random amounts of emergencies. All have the character of attempts to reduce uncertainty, or the consequences of uncertainty in dynamic or time dependent processes. Another kind of uncertainty exists, one having to do not with the dynamics of a process, but with the substance - the actuality of what one is dealing with. This is the kind of uncertainty inherent in problems of screening and diagnosis, and this problem was first brought to our attention by colleagues in public health.

Studies in Screening and Diagnosis

In the midst of our studies of hospital care in the late 1950's, students from the School of Public Health began to appear in our courses in operations research. Among them was Dr. Michel Lechat¹, a leprologist from the then Belgian Congo, bearing a large trunkful of data and a copy of Von Neumann and Morgenstern's "Theory of Games and Economic Behavior" as evidence of his faith that quantitative analysis might help some of the problems of control of tropical diseases. The specific problem troubling Dr. Lechat was the overwhelming load on the ambulatory care services for leprosy - the "clinics under the trees". The development, during the 1940's of the sulfones for treatment and control of lepromatous leprosy had made outpatient care possible, and this brought on a dramatic increase in the number of persons who presented themselves for screening and care. The traditional procedure for screening for contagious cases involved the preparation of 10-20

¹ Dr. Lechat had been Medical Director of the Leprosarium at Cocquiatville.

tissue smears for microscopic examination. Laboratory resources were swamped. The questions were, could fewer tissue smears detect cases with adequate sensitivity, and if so what number of slides would maximize the rate of detection of contagious cases. The answer lay, it was hoped, in the trunk, with its screening data on hundreds of contagious cases.

The answer to the second question was found with little trouble. After some painstaking search for patterns of appearance of lepromatous bacilli in tissues smear slides from various sites, it became apparent that one slide could detect 80% of the cases. Combining this knowledge with some work studies of laboratory preparation and examination of slides, we determined that, for fixed laboratory capacity, case detection rate was maximized with one slide (Flagle and Lechat, 1961), but the ethical question was raised of the adequacy of a test with 80% sensitivity, implying that 20% of the true positives would be missed. Adding slides to the screening procedures increased sensitivity, thereby detecting more cases among those examined, but losing cases among those who were excluded from examination by limited capacity of the laboratories.

We formulated the problem in decision theoretic terms, as a game against nature (Lechat and Flagle, 1962) which forced us to make some estimates of the costs associated with the missed case. It happened that the marginal contribution of a second slide was substantial, placing administrative pressure on an increase in laboratory capacity.

The experience gave us a healthy respect for the magnitude of the problem of estimating costs of missed cases. In some later efforts to find optimal screening strategies, that is to say to determine the choice of level of a screening measure that minimizes the total costs or regrets of associated with false negatives and false positives, it became apparent that there is no single threshold of a screening measure that is universally optimal (Flagle, 1965). The optimal threshold is a function of both of the prevalence of undetected disease in the population screened and the ratio of costs of false positives and false negatives, all ephemeral quantities, not knowable with confidence. However, the importance of these numbers diminished as the sensitivity and specificity are increased jointly. This forces better screening procedures than the traditional approach of basing decisions on the results of a single test, seeking a tradeoff between sensitivity and specificity. One approach to improvement has been to search for patterns of several key variables, perhaps in conjunction with the screening test, which increase the accuracy of detection.

To do this requires statistical analysis of a data base containing a number of true positives and true negatives, itself a process requiring computational power (Gleser and Collen, 1972) (Lincoln and Parker, 1967). Beyond that there must be a medical record system in operation in a screening clinic to capture measures of the key variables and to recognize significant patterns related to diseases. In these early approaches to using statistical methods to improve the accuracy of screening and diagnosis and to automate the analytic processes as an integral part of records keeping, we see some of the beginnings of the domain of medical decision making in the field of medical informatics.

Conclusions

All the reminiscences mentioned so far have been culled from experiences at the clinical or administrative levels of direct health services. This is where exciting work has been done and is being done. However, the picture would be incomplete without some mention of the efforts to build information systems for decision making at community state and national levels. Historically, such efforts were an integral part of the Hill-Burton Program, which demanded from an applicant for hospital construction funds a community based plan demonstrating the need for new facilities. Further, the concept of progressive patient care, as endorsed by the Public Health Service, envisioned the hospital as the center of a coordinated set of comprehensive services. The technique of patient classification had the purpose not only of assignment of patients to appropriate levels of care within the hospital but, in addition, to promote organizational ties with various forms of rehabilitation and extended care. This form of vertical integration, shaped by comprehensive health planning, it was hoped, would replace the traditional "non-system" of "fragmented services". As we know, the non-system, successfully resisted vertical integration for a long time. Only recently, under the pressures of per case reimbursement - made possible by the information systems growing out of patient classification - have we seen a trend toward hospital initiatives in comprehensive services. It is interesting to recall that the development of information systems for comprehensive community health services part of the stream of developments in the Hill-Burton Program. Computer based patient flow simulation models - deterministic rather than stochastic - have been in use for years to forecast trends in health services demand and manpower needs. Somehow these activities, which influence decision making at policy levels, rather than clinical and institutional levels, has not yet become a major interest in medical informatics. However, in the long run the knowledge

gained from the research in medical informatics of clinical level will be drawn upon for refinement of decision processes at policy levels - and this will be another challenge for the evolving field of medical informatics.

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HISTORY OF THE TDS MEDICAL INFORMATION SYSTEM

Melville H. Hodge

1. Introduction

The application of computer and communication technology to medicine - medical informatics - may be viewed from several perspectives. Application of this technology may range from the molecular level to the individual patient or clinical level and ultimately to the health care delivery system level. Alternatively, a motivational perspective reveals objectives ranging from academic research directed toward publication to enhancement of the investigator's practice or his institution's performance to a profit motive. Assessment of any given medical informatics undertaking must necessarily be in the context of these perspectives.

The TDS Medical Information System - known as MIS - is perhaps both the earliest and currently most comprehensive professionally oriented hospital information system in widespread commercial use, ranging from suburban community hospitals to major tertiary teaching and research institutions. Its scope has been the hospital, or group of hospitals, and increasingly, the outpatient, or ambulatory, patient population served by those hospitals. The motivation of its builders has been to provide measurable economic benefits to its users exceeding its costs, resulting in a shared net economic benefit sufficient both to provide an incentive to users to acquire MIS and a return on investment to its builders to continually attract capital for system enhancements and further installations.

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Our purpose here is to describe MIS, record its history which generally spans the entire epoch of medical informatics, consider its contributions to both patient care and to computer technology and finally, speculate briefly about the future.

2. MIS Description

The unwavering goals of MIS have been to reduce costs and improve patient care. Economic considerations in health care are often fuzzy; phrases such as "improved productivity", "increased efficiency" and the like abound. The unambiguous goal of MIS is to provide "cost-lowering technology" to the hospital resulting in the total value of checks written by the hospital to employees and suppliers (including the MIS supplier) are lower after its installation than prior to its installation.

The patient care objective, unfortunately, for a system purporting to impact an entire health care delivery system such as a hospital with patients whose ills may span the entire gamut of ailments and injuries afflicting humankind has not thus far been amenable to "outcomes" studies. Instead, patient care enhancements must be measured by improvements in input variables intuitively related to improved outcomes such as error reduction, timeliness enhancement and improved, and even structured, information availability for clinical decision making.

The visitor to a MIS hospital would find cathode ray tube (CRT) terminals and printers located at all hospital work sites and interfaces to specialized systems (e.g. clinical laboratory systems), all connected to a large computer located in the hospital, or alternatively, in a remote regional center serving multiple hospitals. These components appear at least superficially similar to other commercial systems in other hospitals. On closer examination, however, the unique characteristics of MIS would begin to

emerge - extensive direct use of terminals by physicians, nurses and other professionals and patient chart content consisting up to 80% or more of MIS printer-produced documents attesting to a predominantly "on-line" patient record.

The observer at a nursing station would witness a physician using a CRT terminal with light pen menu selection providing fractional second display responses. Screen content would be entirely in standard medical terminology with no special coding or "computerese". This content might be general, organized by medical specialty, personalized in "order sets" for each physician or, in research settings such as the NIH Clinical Center, representing extensive research protocols. Nurses would be observed charting through the same terminals and working from system-produced patient care plans. None of the traditional documents associated with the nursing station such as order sheets, kardexes, medication slips, requisitions or the like could be found. IV scheduling, acuity-based staffing and numerous other supports to nursing would be evident.

The usually incessant telephone ringing at nursing stations and in ancillary departments would be absent as status information is readily available through any terminal. Physicians entering the hospital would use the first terminal they encounter to do "electronic rounds", reviewing the up-to-the-minute reported clinical status of all of their patients in the hospital and planning their rounds based on that information. Ancillary department work lists, labels, requisitions and the like would be automatically produced on department-controlled schedules. Medical record indexing and abstracting would be automated.

Since all patient care transactions are captured at their source, data entry into hospital financial systems is automatic, feeding sophisticated multi-tiered insurance proration systems, cash management systems and the like. Spanning both the clinical and the financial systems is a powerful fourth generation distributed relational data base capability for ad hoc decision support, permitting hospital executives to employ advanced quantitative tools in matters such as PPO pricing, resource requirement forecasts, cost analysis, etc.

Visiting other MIS hospitals in the U.S., Canada or the U.K., our observer would be struck by great differences in functionality and usage as all terminal displays, reports, schedules and applications are matched to the unique needs of each hospital and are independent of underlying MIS software. Despite their diversity, MIS hospitals, at least those that have undertaken formal studies, share

certain common results - reduced costs, shorter patient stays and markedly reduced error rates.

3. Origin and Objectives

If a single word must be selected to characterize the men and women who collectively created present day MIS (now the foundation of TDS Healthcare Systems Corporation's Health Care 4000 System) it is perseverance.

The origins of MIS may be traced to the Lockheed Missiles & Space Company in Sunnyvale, California in the early 1960s - then, as now, the nation's largest missile and satellite contractor. From a need to diversify from this enviable, but at the same time vulnerable, position came a decision to exploit then fledgling computer-communications technology by applying it to hospitals. Omniscient counsel in reaching this decision came from the late Dr. Raymond White, Director of Socio-economic affairs for the American Medical Association, the late Dr. Howard Aiken, founder and director of the Computation Laboratory at Harvard and the late Dr. Clarence Lovell, Director of Switching Systems at the Bell Telephone Laboratories.

The Lockheed Information Systems Division was born in 1964 and staffed by a small group of technically capable, but medically naive managers, engineers and analysts. Reflecting their aerospace backgrounds of seeing desired achievement limited only by their collective ability to solve perceived technical problems, this group faced a then uncomprehended education in the many non-technical factors which control progress in health care institutions. Applying aerospace systems analysis skills, the potential economic benefits of automating information flow in the hospital were quantified with Public Health Service contract support, convincing the Lockheed group that their objective was economically feasible.

In 1966 this group was invited under contract to assist the Mayo Clinic in a comprehensive assessment of computer system needs of the Clinic and its two associated hospitals. Twelve Lockheed engineers worked intimately with a like number of Mayo Clinic physicians for two years in Rochester, resulting in development and experimental use of a three-terminal prototype of MIS, a proposal for development of an operational system submitted by the Mayo Clinic to the (then) Department of Health, Education & Welfare which was not funded and finally, twelve no longer medically naive Lockheed engineers returning to Sunnyvale with a more sophisticated view of the needs of a physician-oriented medical information system.

Lockheed management, lead by Herschel Brown, its Executive Vice President, and Kenneth Larkin, its Information Systems Director, then decided to fund the commercial development of MIS. El Camino Hospital in Mountain View under the leadership of R. Edwin Hawkins agreed to serve as the development site. By 1971 development neared completion (or so it was thought) and operational service contract negotiations between Lockheed and El Camino were initiated. This was a stressful period for Lockheed, however, as it encountered severe difficulties with its C-5A and L-1011 aircraft programs, necessitating curtailment of all discretionary new business programs, including MIS, resulting in a decision to seek an outside equity partner for its fledgling medical division.

Interest was expressed by Technicon Corporation which under the leadership of Edwin C. (Jack) Whitehead had pioneered and then came to dominate automation of the clinical laboratory and which now saw in MIS an opportunity to extend automation from the laboratory to the entire hospital. Partnership with a struggling aerospace company seemed unattractive, however, resulting in outright acquisition of Lockheed Information Systems by Technicon which was then renamed Technicon Medical Information Systems Corporation.

4. Initial Installations

The Technicon acquisition agreement and the El Camino Hospital MIS contract were signed on the same day, May 28, 1971. The El Camino contract was unique in that it provided that the Hospital would pay Technicon only the actual savings experienced by the hospital as measured by a joint Hospital-Technicon cost bureau in which the Hospital reserved the tie-breaking vote. Placing (properly) the full economic risk on Technicon, it also taught the Company an important lesson, that hospital managers, not computer systems, save money. A well designed information system can provide impressive potential cost-benefits, but only motivated hospital managers guided by a carefully prepared benefit realization plan can achieve actual savings.

A threat far graver than economic emerged when the system became operational - massive resistance from important segments of the El Camino medical staff. Spreading quickly from the confines of the hospital to local and even national newspaper headlines, this resistance, initially justified in part by early system shortcomings, seemed intractable. It was countered, however, by the effective leadership of more visionary El Camino physicians, Bryan Shieman, Joseph Ignatius and especially, Ralph Watson, who successively chaired the medical staff MIS

committee, withstood the intense criticism of their colleagues, worked patiently on correcting deficiencies, and converted their colleagues with "hands-on" assistance. Their efforts were supported by the rapidly growing enthusiasm of nurses now freed from paperwork drudgery to the point that physician-opponents alleged that they were being ostracized by nurses for their failure to use MIS!

The (now) Department of Health & Human Services' National Center for Health Services Research played an important role by sponsoring a comprehensive, independent evaluation by the Battelle Columbus Laboratories of the economic and patient care benefits of MIS at El Camino. Believed to be the most exhaustive studies of this kind ever conducted, the Battelle reports¹ clearly supported the views of system proponents.

By 1974 physician acceptance and measured cost savings reached levels resulting in the the Hospital proposing that the old contract be torn up and replaced by a new long term agreement providing that Technicon receive its full fee with the hospital retaining the net savings beyond that fee. Both Technicon and the Hospital had paid a high emotional tuition for a second important lesson, that introduction of technology into a health care delivery setting with impact as pervasive as MIS requires extraordinary attention to the management of change in a human organization. The universal applicability of this lesson has subsequently been demonstrated in numerous other MIS hospital installations. Yet, a present day visitor to El Camino would find all-embracing acceptance of MIS and, indeed, would find no evidence of the slender thread by which its existence hung in the early '70s.

Installation of MIS at the Ralph K. Davies Medical Center in San Francisco in 1972 offered validation of Technicon's regional, multi-hospital center concept, necessary to secure computer equipment economies in an era of high computer costs. This was followed in 1973 by the

¹ Barrett, James P., Barnum, Ronald A., Gordon, Benjamin A. and Pesut, Robert N. "Final Report on Evaluation of the Implementation of a Medical Information System in a General Community Hospital" - Battelle Columbus Laboratories - December 19, 1975

Barrett, James P., Hersch, Philip L. and Caswell, Robert J. "Evaluation of the Impact of the Implementation of the Technicon Medical Information System at El Camino Hospital: Part II: Economic Trends Analysis; Final Report" - Battelle Columbus Laboratories - May 14, 1979

first hospital-operated MIS installation at the Nebraska Methodist Hospital in Omaha..

From its second regional center in Fairfield, N.J., Technicon next installed MIS at New Jersey's largest hospital, St. Barnabas in Livingston. This was quickly followed by the Maine Medical Center in Portland, the first tertiary hospital to employ MIS.

In 1975 Technicon undertook its most challenging installation to date at the Clinical Center of the National Institutes of Health where patient care functions were overlaid by extensive research protocols. Initially operated from the Fairfield center, operations were transferred some years later to the NIH computer facility in Bethesda. Under the leadership of NIH's Thomas Lewis, M.D., the utility of MIS in supporting extensive and sophisticated clinical research has been thoroughly demonstrated.

5. Current Status

In the last decade MIS installations have multiplied. 85 systems have been or are being installed in the United States, Canada and the United Kingdom. These installations include major teaching institutions from coast to coast - New York University, Temple University, Medical College of Virginia, University of Illinois, Loyola University of Chicago, Baylor University, University of California at Irvine and others.

Some institutions acquiring MIS have, in turn, become regional centers serving their own affiliated hospitals or others. Examples include Nebraska Methodist Hospital - Omaha, Hospital Sisters of the Third Order of St. Francis - Peoria, Total Business Systems - Albuquerque and St. Johns Hospital - St. Johns, New Brunswick.

In 1980, Revlon Corporation acquired Technicon Corporation and its subsidiary, Technicon Data Systems (renamed earlier from Technicon Medical Information Systems). Progress slowed under a large, multi-unit company whose diverse interests extended well outside health care. Revlon, in turn, was acquired in December 1985 by Pantry Pride whose avowed purpose was subsequent sale of all of Revlon's health care-related units, providing an opportunity for a successful purchase initiative in August 1986 by John Whitehead, then TDS' president and son of Edwin C. Whitehead. The present TDS (now TDS Healthcare Systems Corporation) Board is comprised of Edwin C. Whitehead, former Technicon Corporation founder/chief executive officer and founder of the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology, John Whitehead, TDS' principal owner and

chief executive officer and the author who had been a TDS founder and its president until 1977. Thus, direction of MIS has been returned to those who have both shared its vision and had a long standing commitment to the health care field.

An important advance in medical informatics at the health care delivery system level is resulting from the initiative of the Department of Defense through its Tri-service Medical Information System program (TRIMIS) to procure a fully integrated system for automation of substantially all information handling in military hospitals and clinics throughout the world. This initiative, named Comprehensive Health Care System (CHCS), has been under study by DOD since 1975. In 1986 Stage I contracts were let to four companies, including TDS, for system development. These contracts were subsequently modified to further provide for operational tests of the four newly developed candidate systems.

While the TDS CHCS system is a new system, it draws heavily on its MIS heritage and on TDS' experience in its successful 1983 MIS installation under TRIMIS contract at the U.S. Army's William Beaumont Hospital in El Paso. The new TDS CHCS system is presently being installed at the Charleston Naval Hospital under the operational test program. DOD has announced that two systems will be selected for Stage II installations in fourteen additional hospitals for extensive evaluation commencing in 1988. TDS subcontractor-partners include IBM, AT&T and Computer Sciences Corporation.

MIS has been continually updated to state-of-the-art computer technology, and is provided in a wide variety of IBM computer and operating system configurations, ranging from the IBM 9370 to the IBM 3081 under the DOS-VSE, MVS-SP1, MVS-SP2 and VM operating systems. This architecture supports the fully integrated Health Care System 4000 which combines patient care, patient administration, patient accounting and decision support functions.

Under experienced, health care-oriented ownership, TDS has overcome the stagnation encountered in the latter period of Revlon ownership and sale. A number of significant product enhancements were introduced in 1987, and hospitals are contracting for TDS systems in accelerating numbers.

The growing, loyal group of hospitals who have adopted MIS as the foundation for automating information processing in their institutions have played an important role in the furtherance of MIS through MISA, perhaps the most effective hospital user's group in the industry.

6. Impact on Health Care Delivery

The first objective of MIS, to permit hospitals to achieve an absolute reduction in costs,² has been achieved and independently documented in numerous hospitals. The chief executive officer of El Camino Hospital, the first MIS installation, reported in 1985, "Ten years later, the savings have multiplied to an approximate value of \$20-\$21 per patient day. These savings are above and beyond the cost of the system itself... The hospital in-patient cost per case is 40% less than the county average for 13 similar community hospitals."³ The chief executive officer of the second MIS hospital, the Ralph K. Davies Medical Center, reported savings of \$9 per patient day as early as 1976.⁴ Waukesha Memorial Hospital has reported achievement of originally targeted savings of \$2.5 million over the initial seven year period. Despite a reduction in census from 298 to 218 following installation of MIS, this hospital reports the lowest cost per patient day and the lowest number of full time equivalent employees per adjusted patient day for a hospital its size in the State of Wisconsin. Studies at The Medical Center of Central Georgia reported that, "...extended cost benefit of the HIS (MIS) for a cumulative seven years is over \$13,000,000."⁶ An independent analysis performed at the National Institutes of Health Clinical Center reported that, "The results of the cost-benefit analysis show that MIS provides greater benefits than

2 For a discussion of economic con-
siderations differentiating cost-
lowering technology from cost-
increasing technology, see Hodge,
Melville H. Medical Information Sys-
tems - Aspen Systems, 1977

3 tems - Aspen Systems, 1977
Buchanan, Neilson S. and Norris, Jim
"A Businesslike Hospital Gets
Business's Attention". Health Cost
Management - Vol 2 No 3 - May/June
1985

4 Private communication from George D. Monardo, President, Ralph K. Davies Medical Center to A.L.(Jack) Kahn, President, Methodist Hospital of Indiana - January 30, 1976.

5 Indiana January 30, 1976.
Blask, Dan and Miller, Gale "A Computerized Medical Information System can be Cost Effective" - Healthcare Computing & Communications - April 1984

Blask, Dan; Cleary, Jack and Dux, Larry "A Computerized Medical Information System - Sustaining Benefits Previously Achieved" Healthcare Computing & Communications - December 1985

6 Carter, Larry A. "The Hospital Information System - A Weapon for Survival under DRG's" American Hospital Association - Copyright 1984

less automated alternatives, that the value of the benefits it provides exceeds the costs of the system, and that the net value (i.e., value minus cost) of MIS is greater than⁷ that of less automated alternatives."

As noted elsewhere, achievement of impressive savings is the consequence of management action in effectively using a powerful tool, not merely the result of installing a computer system. Management engineering analysis reveal the sources of these savings.

1. Realized labor savings - In a now classic 1966 paper Jydstrup and Gross assessed the substantial labor investment of hospitals in information processing and estimated that 24% of the total cost of operating the hospitals which they studied were attributable to such activities.

The opportunity for substantial labor displacement is suggested by Figures 1 and 2, below:

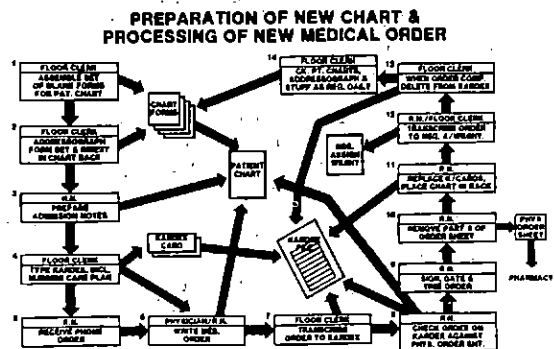


Figure- 1

Figure 1 flow charts a single hospital information processing task - preparation of a new chart and processing a telephoned medical order for the new patient - as it is typically performed manually.

7 Blackmon, Paul W. "Evaluation of the Medical Information System at the NIH Clinical Center - Volume I Summary of Findings and Recommendations" Analytic Services, Inc. - January 1982

8 Services, Inc. - January 1982
Jydstrup, Ronald A. and Gross, Malvern
J. "Cost of Information Handling in
Hospitals" - Health Services Research
- Winter 1966

PREPARATION OF NEW CHART & PROCESSING OF NEW MEDICAL ORDER

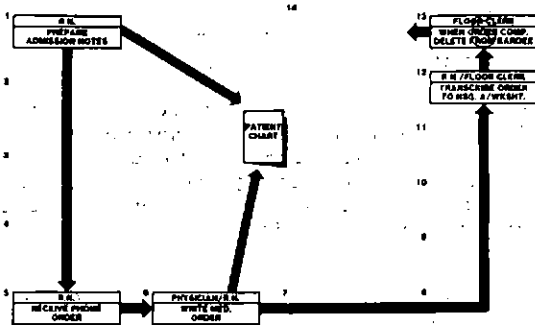


Figure 2

Figure 2 flow charts the same process following the installation of MIS. By estimating times for each eliminated task, multiplying by task volumes and replicating this process for each hospital task affected by MIS, an estimate of potential savings by skill category, work site and shift is obtained. Then, working with affected managers and supervisors, practical work force adjustments are planned, resulting in realizable savings, typically ranging from 50-70% of potential savings.

2. Reduction in length of patient stay - The Battelle study documented a 10% length of stay reduction attributable to MIS, resulting primarily from substantially reduced test turn-around times. Under prospective payment, length of stay reductions have a significant impact. For example, a 5% reduction in length of stay in a 300 bed hospital with 30% fixed payment patients (e.g. DRG and HMO) will result in a \$67,500 per month savings.
3. Reduction in forms usage - Elimination of manual information processing tasks as suggested by Figure 2 also eliminates associated forms. Additional pre-printed, often multi-part, forms are replaced with less expensive MIS-printed documents. Forms savings of \$5,000 per month or more are not unusual.
4. Advance of billing date - Advancing the billing date three days in a 300 bed hospital results in a one-time revenue capture of \$385,000, or \$3,200 per month, assuming a 10% return on capital.
5. Reduction in wasted meals and supplies - Up-to-the-minute information on patient bed location and diet orders substantially eliminates misdirected

or inappropriate meal trays. Similarly, waste of requisitioned materials, including drugs, is substantially reduced.

6. Reduction in bad debt losses - By flagging patients with poor payment histories in a long term MIS file, one 750 bed hospital estimated a bad debt saving of \$41,000 per month.
7. Reduced rework resulting from fewer errors - In addition to the patient care implications of error reduction (discussed below), a corollary result is avoiding the need to repeat a task. For example, the patient transported to radiology for an upper GI series and then found to have eaten breakfast must be rescheduled after dieting; this kind of error is virtually non-existent in MIS hospitals.

In addition to the more easily quantifiable economic benefits which have been reported, additional contributions to hospital economic performance may result from improved decision making resulting from more accurate, complete and timely information, better resource allocation resulting from "real time" visibility into needs and more timely and comprehensive performance monitoring permitting immediate and precise corrective action.

Assessment of patient care improvements must rely on improvements in input variables plausibly related to better care as suggested earlier, admittedly a less satisfying approach than the conceptually preferable but thus far impractical use of outcomes studies. This methodological limitation does not mean that such improvements are any less real, only that they may not be directly quantified.

A comparison of pre- and post-MIS medical records at New York University Medical Center demonstrated a 22% reduction in physician medications orders omitting site, route of application or schedule, a 6% reduction in orders that were hard to read, a 2% reduction in ambiguous pharmacy and radiology orders and a 32% reduction in radiology orders omitting clinical indication.¹⁰ A study at Georgetown University Hospital (not a MIS site) reported 16% of the handwritten words in physician progress notes were illegible as were 8% of physician signatures. Comprehension losses of greater than 5% were measured on 12% of the progress note found

⁹ Barrett, et al - ibid

¹⁰ Grams, Stanley, Grieco, Anthony, and Williams, Robert "Physician Use of the Technicon MIS Provides Major Benefits and Savings to New York University Medical Center" - (in press)

¹¹ White, Karen B. and Beary, John F. New England Journal of Medicine -

in patient charts.¹¹ Nursing and ancillary error reduction has also been measured. At NYU, MIS resulted in a 22% reduction in medication site and route charting omissions, a 10% reduction in radiology schedule variances and a 16% reduction in laboratory schedule variances.¹²

Undoubtedly, the consequences of most of these measured errors are trivial; however, patient care in a high error environment must necessarily be considered to be at some risk. The contribution to patient care of other error-reducing components of MIS such as automatic drug-drug interaction monitoring and IV administration monitoring have not thus far been measured, but also lead toward a more error-free environment.

Improved timeliness may also contribute to patient care as well as being economically important by contributing to reduced length of stay. The NYU study measured reduction in departmental ordering turnaround times:¹³

Department	Hours	%
Pharmacy	4.9	71
Radiology	9.0	8
ECG	6.1	14
Hematology	4.4	22
Chemistry	2.4	9
Microbiology	4.6	4

More efficient use of physician time, while representing an economic benefit to the hospital only in the case of house staff, may have a favorable effect on care. "Electronic rounds" from any hospital MIS terminal (or increasingly, from a terminal located remotely in the physician's office) result in more frequent and timely monitoring of status and more efficient planning by the physician of his hospital itinerary.

Most MIS hospitals have implemented impressive care planning systems produced by the system, integrating physician orders and nursing inputs. Nursing staffing reports result in continually adjusted staffing to meet changing patient care needs. Communication between nurses, particularly between shifts, is greatly enhanced by care planning and status reports.

Finally, use of MIS shifts the physician from a mental process of reliance solely on recall from memory to one of recognition from among presented alternatives. These alternatives may be general, specific to a given specialty or even personalized by and for each physician for a variety of clinical situations. In an

ever more complex medical information environment, it seems indisputable that the synergistic partnership between the enormous information storage and manipulation capabilities of the information system and the superior decision making capabilities of the physician contribute importantly to a level of patient care unattainable in a purely manual information processing environment.

7. Impact on Computer Technology

Given its commercial objectives, publication concerning the technical aspects of MIS has never been encouraged. The unsettled nature of law concerning property rights in software necessitated a policy of trade secrecy rather than patents or copyrights. Hence, technology transfer from MIS has been limited; similarly, no effort has been made to trace MIS technology migration into other systems. Subject to the limitations suggested by the foregoing, it is believed that a number of important concepts were pioneered or furthered in the development of MIS. While TDS' present day Health Care System 4000 represents the combined contribution of hundreds of dedicated men and women, the key underlying concepts predominantly reflect the genius of Paul Williams - the most outstanding system design "philosopher" with whom the author has ever worked, Charles Tapella, a brilliant systems architect and Bradner Hisey, M.D. whose unusual perception of the needs of his profession combined with outstanding computer systems insights.

The unwavering commitment to providing a system capable of direct use by medical professionals served as the stimulant for several of the most important of these concepts. It was the belief of MIS developers that the system must meet the physician (or nurse) on his/her own terms, that is, require no special knowledge (codes, etc), function in the natural language and vocabulary of the user (medical English), require no special skills (typing) or increase the time required by the user to perform his/her encounters with the system contrasted with that required for the corresponding tasks in a manual paper environment. While it was believed that important and attractive benefits could be provided to the professional user through application programs, challenge was design of a terminal subsystem which professional users could be induced to utilize voluntarily, discarding their traditional dependence on ward clerks, or other intermediaries for information processing.

To meet this challenge, the first commercial use of the CRT/light pen terminal with menu selection was developed, chosen over the typewriter keyboard terminal (special skill requirement), the

¹² February 6, 1986
¹³ Grams, et al - ibid
Grams, et al - ibid

template keyboard (cumbersome and inflexible), the touch screen terminal (choices limited by finger dexterity, finger shading, screen contamination), mouse/trackball (hand/eye coordination reduces speed well below the light pen, limited terminal location work surface availability) and speech recognition (then primitive, high ambiguity and error potential). This choice has withstood more than two decades of experience without being obsoleted by a superior technique.

Professional acceptance was found to require extremely fast terminal response to light pen selections to avoid user impatience. Based on experiments conducted with Mayo Clinic physicians it was found necessary to keep response time within the "thinking time" of the physician as he contemplated successive selections; it was essential that his clinical thought processes not be intruded upon by a need to wait for a system response. A response requirement of 0.4 seconds was established for peak hour system loading (later, it was found necessary to contractually guarantee response times subject to penalties). This response was provided in a mainframe environment by segregating terminal handling from applications processing, assigning highest priority to terminal handling and performing all edits on the input message prior to transferring the input message to the applications processor. This latter step also permitted immediate return of "edit ok" messages to users, allowing them to leave their terminals without risk. This response time was believed to be unparalleled for many years, and even today is unusual in hospital information systems where terminal handling and applications processing are typically intermixed.

Perhaps as important as response time is the need to absolutely assure medical professionals of data integrity. Given a world in which both equipment failures and software "bugs" are inescapable, MIS developers created a "soft recovery" system in addition to the customary transaction tape-based "hard recovery" system. The soft recovery system created a system synchronization point at defined intervals (say, five minutes), quiesced the task queue, and wrote old records to a predecessor file. In the event of a failure the predecessor file records were overwritten into the main file and the task queue was reprocessed, omitting the offending transaction (usually the consequence of a software "bug") which was output with an appropriate error message. Soft recovery times of perhaps 30 seconds contrast vividly with the conventional hard recovery times of several hours. It is understood that this technique has been more recently applied in other systems.

Another pioneering technique was the matching of each applications display with

a corresponding "Type II" hidden display or directory which contained data coding of each element on the display. This permitted creation of completely generic applications programs free of any function-specific content. This, in turn, contributed enormously to system generality. Thus, MIS represented an early (perhaps the earliest) relational data base system with variable length fields.

For regional hospital operations, high speed (56 kb) lines were employed with a MIS-developed, highly efficient, thoroughly reliable protocol. Now, in an era when computer costs continue to plummet the efficiency of these techniques is no longer required to maintain reasonable system costs. The multi-hospital processing capabilities have, however, proven extremely useful in the presence of modern multi-hospital organizational trends.

8. Business Perspective

From a technical and functional performance perspective, MIS has been judged to be highly successful by most observers, a conclusion even confirmed privately by some of TDS' most vigorous competitors. It has been less successful, however, from a business perspective. This management shortcoming is attributable primarily to mismatching TDS' products to the needs of the hospital marketplace.

In 1966 the Medicare and Medicaid amendments to the Social Security Act were enacted as a centerpiece of President Lyndon Johnson's Great Society. While the Federal government had previously exercised some influence over the private sector hospital community through the Hill-Burton program for hospital construction funding, the 1966 landmark Medicare legislation suddenly thrust the Federal government into the role of principal third-party payor of hospital bills. It elected to exercise its newfound power through a cost reimbursement system.

The hospital community responded by demanding systems for charge collection and patient billing from the computer services industry. Hospitals (and their computer vendors) prided themselves on their ability to charge for a single cotton ball even though little management information was available permitting control to be exercised over the nursing department payroll, representing about half of the total cost of operating the typical hospital! It was an era when revenue equalled costs plus...

A number of hospital computer services companies were created in response to this new Federally created need; perhaps Shared Medical Systems and the McDonnell-Douglas Automation Company have been the most successful, attracting hundreds of shared

patient billing accounts. Meanwhile, the TDS team (under its earlier Lockheed banner) was deeply engrossed in system design to absolutely reduce hospital costs and provide better patient care. Regrettably, this focus was unresponsive to the then perceived needs of most hospitals. Given the vital dependence of hospitals on patient billing and Medicare accounting, hospital chief financial officers emerged as the dominant executives controlling their institutions' computer system acquisitions. Physicians, nurses and other health care professionals, TDS' natural constituency, had little influence over these acquisitions. Exceptions occurred mainly in institutions headed by unusually strong chief executive officers who saw their role as one of partnership with medical professionals to bring lower costs and better care to the population they served.

The Government's cost reimbursement policies produced an enormous escalation in health care costs. Efforts were undertaken to find an alternative. In 1983 a system of prospective payment by diagnosis-related group (DRG) developed at Yale University in the early '70s was adopted by the Health Care Finance Administration for Federally-funded care. As this system was adopted and its implications understood it became apparent that a sick person in the hospital, formerly an asset, was now a liability. To do as little for him (or to him) and get rid of him as soon as possible became the new strategy. Further, cost reduction, formerly seen simply as a path to revenue reduction, came to be seen as a new strategy for economic survival and even profitability.

Thus, it now appears that MIS represents a concept whose time has come. From a business standpoint it is regrettable that TDS did not attune its offerings more to the needs of the marketplace it elected to serve. Had it done so, however, it is unlikely that the resultant orientation to enter hospitals through the business office door rather than the medical staff door would have ever permitted building an organization committed to what good system design practice seemed to dictate back in the sixties, enhancing the capability of the hospital and its medical staff to carry out their primary mission - to strive in an efficient manner to make the sick well!

9. Outlook

It is often said that those who do not learn from history will be forced to relive it. It seems unlikely, however, that the future of medical informatics at the health care delivery system level will be merely a cyclical repetition of the past, nor even a linear extrapolation of

past trends. Our lessons concerning the penalties associated with failure to accurately divine the needs of the hospital marketplace as they may exist at any point in time makes it seem imperative not to sidestep the task of considering the likely future nature and role of a system such as MIS.

First, past battles of professional acceptance and achieving important net savings will not have to be refought at the conceptual level. It is imperative, however, to never forget that introduction of MIS into a new hospital profoundly impacts a human organization to perhaps an unparalleled degree. If the need to manage the change process is ignored, resistance and even rebellion may be reasonably predicted. The business of doctors is not to make computer systems successful; success has repeatedly been demonstrated to be the consequence of each doctor, one at a time, coming to see how his performance is enhanced and his hospital practice facilitated by investing his always scarce time in learning how to use MIS efficiently. Similarly, hospital managers, not computer systems, reduce costs when they employ fewer people and order fewer goods in carrying out their missions. Since these actions are counterinstinctual to experience when the goal is a high level of performance, hospital managers must both participate in and "buy into" a carefully designed benefits realization program before they can be reasonably expected to act.

It seems likely that the future will find increasing structure in the practice of medicine. The unrelenting pressure of third party payors led by the Federal government appears to be leading toward the eventual imposition of standards of care. It would not be unexpected to see the pioneering work of Dr. Lawrence Weed on the problem-oriented medical record find rebirth, perhaps in a metamorphosed form. Physician-oriented systems such as MIS seem to be the appropriate vehicle to support such trends.

Progress in medicine appears to be leading to the same conclusion. Newer modalities of diagnosis and therapy are often sufficiently complex and require a degree of coordination among health care professionals sufficient to obsolete conventional methods of information processing and coordination.

The pressures cited above may also focus providers on clinical benefit vs. cost tradeoffs. Perhaps the day will come when physician ordering displays will present costs along with indications, contraindications, adverse interactions and side effects and the like for consideration in the formulation of a diagnostic or treatment program. Cost staging may be routinely correlated with disease staging.

Performance evaluation and audit is likely to become more sophisticated with the widespread advent of the on-line medical record. Emphasis will increase on truly concurrent review to permit timely intervention.

Hospital managers will employ system-produced data in sophisticated resource allocation processes. Hospital data and external data will be accessible to hospital executives for use in market segmentation, bidding on preferred provider contracts, service pricing and the like.

Strategic planning by hospitals may, in fact, be necessary strategic survival. Under intense pressure from a society that is no longer tolerant of health care cost escalation outstripping national income growth, only three out of five present hospitals may exist ten years from now. The capacity of the hospital to foresee community needs and accurately match its services to those needs in a competitive environment is likely to make comprehensive, powerful decision support systems seem indispensable.

The objectives of improved patient care at a lower cost set for MIS more than twenty years ago seem even more relevant for the 1990's. If a single lesson is drawn from the brief history of medical informatics at the health care delivery system level it is that despite errors in both judgement and execution along the way it has proven to be worth doing. Medical historians have suggested that medicine crossed the boundary from doing more harm than good to the inverse sometime around 1940. Perhaps, insufficient time has elapsed to permit a similar judgement about medical informatics applied to the health care delivery system. But one might be permitted to say the signs are encouraging!

PATIENT MANAGEMENT SYSTEMS: The Early Years

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As I scanned through old papers and reports in preparation for these remarks, I became depressed in the "sameness" of those proposals and descriptions with what is happening today. Then I realized there are major differences - today's systems work and are affordable.

The health care delivery system is an industry whose magnitude, complexity and pervasiveness are rarely acknowledged. In a few decades, the industry has literally changed from a cottage industry to a multi-billion dollar giant with whom every individual in our society has come into contact. It is a personal industry, yet at the same time, one of our most technically sophisticated industries. It is not surprising that computers are becoming an integral part of that system. This paper discusses some of the experiences in reaching that goal.

As a beginning engineer back in the

1960s, I, with many others, felt that the development of computerized patient management systems was not only natural but mandatory. One merely needs to observe the process to realize that keeping track of what was done and charging appropriately, of sending information from one place to another, of storing data and printing it on demand, and of controlling process and flow are tasks which computers perform well. Many medical specialties already used forms for the collection of data. Most medical knowledge was already clearly identified in textbooks, including what questions to ask, what parameters to measure, what tests to order, how to diagnose, and how to treat. "A simple matter of programming" was a phrase often used and believed. It later became a standing joke. Many predicted that the use of computers for medical applications would develop into a multi-million dollar market whose potential would be quickly realized. The actual events proved to be quite different.

The development of patient management systems has been influenced by several

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factors. The first, and perhaps one of the most significant factors, is that of technology - hardware and software. During this development period, computers evolved from single tasking, "untouchable" and "unfriendly" mainframes to highly interactive, multiuser minicomputers.

A second factor is that of the people involved - both the developers and the users. The developers had to learn first what to do and how to do it and then learn how to package and sell it to the ultimate user.

Economic factors also influenced progress. As computer costs decreased, the cost of delivering patient care increased. Computers seem to be offer one way to reduce and control these costs.

Another factor was the tremendous increase in the amount of data generated and the demand for that data by a variety of individuals. For example, both the number of laboratory tests available and the number of tests actually ordered increased exponentially during this period. Estimates on the costs of information handling vary between 25 and 39% of the total cost of health care [1]. With the influx of many research dollars from NIH, actual medical knowledge increased.

Finally, the influence of external factors such as the government and third party payors contributed significantly to the development of patient management systems. As one observer commented [2], "I think that just as the Medicare legislation forced hospitals, almost

without exception, to use the computer for financial processing, patient accounting, and patient billing, the PSRO type of thing - which will get built on more and more, particularly with national health insurance likely to go in within the next year - will force computerization of the clinical side of the hospital."

The digital computer became available for general use in the late 1950s. These first systems provided few user-oriented features and required considerable knowledge and skill to use. Early systems were batch oriented and supported single tasking only. These computers were large, required specially prepared spaces, and were quite expensive. In addition to machine language, followed by assembly language, only Fortran and Cobol were available as higher level languages. Most programs were written by computer specialists who had only limited interaction with those who would ultimately use the systems. The reliability of early systems left much to be desired. Hardware failures were the norm rather than the exception. Software crashes were commonplace. Perhaps life with these early systems was best described as "working with a machine you couldn't touch; working with a machine that didn't work; working with a machine that you couldn't afford; and working with systems that were not useful."

I shared office space with two cardiology fellows who seemed to spend most of their day making meticulous measurements of amplitudes and time

durations of the various waveforms of the ECG. After recording these carefully on paper, they applied a set of rules to interpret the ECG readings. This task seemed to me to be a simple engineering problem which could be solved almost trivially by a computer. Unfortunately there were the problems of noise, wandering baselines, arrhythmias and PVC's, variations in patterns and other factors to solve to produce the same result as the human. Researchers quickly learned that it was difficult to teach the computer to recognize patterns which were easily identified by humans [3, 4, 5].

Gordon [6] points out difficulties of attempting to overlay the computer's orderly, pedantic and, indeed, binary world with the softness, variability and "between the lines implications" of medical data under human direction - a point that is still valid. He notes that the adoption of computer technology in practice must be concerned with the customs of 200,000 physicians serving independently or in 7,000 hospitals and clinics. Changes from manual documentation to automated procedures are often bewildering and ineffective.

The early development of patient management systems was supported primarily by NIH grants. Since 1968, the National Center for Health Services Research has played a major role in supporting the development, application and evaluation of patient management systems [7]. No hospital could afford a computer. Since the funding came from external sources,

developers often did what they wanted to do and how they wanted to do it, rather than interfacing with users who wanted to have nothing to do with the system in the first place.

Developers were consistent in their reasons for developing patient care systems. Almost all papers or proposals started with a line, "We are currently in the midst of a health-care crisis. The average cost of a hospital bed has tripled since 1957." Systems were proposed to reduce the costs of patient care, to reduce length of stay, to improve patient care, to improve nursing care, to improve communication, and to improve decision making. Little evaluation was done. For the most part, we did what we knew how to do and wrote research papers to justify it.

Melville H. Hodge sets the stage for this period in the Preface of his book Medical Information Systems [8]. He states that, in the early 1960s, a small group of hospitals became identified with one common goal, that of a commitment to serve as a site for the development of computerized handling of patient information. Some of these early hospitals include Akron Childrens' Hospital in Ohio; El Camino in Mountain View, California; Baptist in Beaumont, Texas; St. Francis in Peoria, Illinois; Charlotte Memorial in North Carolina; Washington Veteran's Administration Hospital; Henry Ford Hospital, Detroit, Michigan; Monmouth Medical Center, Long Branch, N.J.; Mary's Help Hospital, Daly

City, California; Deaconess Hospital, Livingston, Indiana; Latter Day Saints Hospital, Salt Lake City, Utah; and Downstate Medical Center, New York City, New York. We owe a debt of gratitude to these early pioneers, and I might say suffering sites.

Most major computer companies, such as IBM, Burroughs, Control Data, Honeywell and NCR, seeing the potential of significant sales, were active in their support. Industries experienced in using computers to manage complex systems joined in. Some of these companies include Lockheed, who supported the early development of the Technicon Hospital Information System; McDonnell-Douglas, who is still active in the field; and other companies, such as GE, who later abandoned these efforts. Most of these systems were well reported in the literature (See, for example [9,10]).

Many groups in Europe were developing systems at the same time: the Danderyd Hospital [11] and Karolinska Hospital [12] in Sweden; London Hospital [13] and Kings Hospital [14] in England; and the Hanover Hospital [15] in Germany to mention a few.

Unfortunately, most of these early systems resulted in resounding failures. The reason primarily for these failures and for the slow progress into the 1970s was largely due to underestimating the complexity of the information requirements of patient management systems. Furthermore, users, as contrasted to developers, were not involved at an

adequate level and, in fact, were not ready for computers. Hardware and software tools were inadequate. Hospitals felt that they had been oversold an unattainable product, and, at the loss of millions of dollars, abandoned their efforts in computerization. As Hodge notes, optimism and enthusiasm was replaced by skepticism and then cynicism.

Fortunately others persisted. As technology advanced, driven by the space efforts of the '60s, developers learned to appreciate the complexity of the problem and began to address smaller, more easily defined components of the overall system. A few successes appeared, although some projects failed in the transition from carefully nurtured demonstration projects into systems which interfaced with, usually, the least paid, least motivated, and least educated employees of the medical support staff.

By the early 1970s, however, some of these early systems, after years of development and many more development dollars than anyone anticipated, became commercially available [16,17]. After a period of overpromise and underachievement, some progress could be noted [18].

The Technicon system, begun by Lockheed in the 1960s, was installed at the El Camino Hospital in Mountain View, California and became, perhaps, the best known "successful" application. The "success" of this system in its early years at El Camino can perhaps be measured by an article in the October 1973 issue of

DATAMATION [19]. El Camino was truly a guinea pig in the development of the hospital information system and suffered through the many bugs. During the first year of installation, more than 2000 changes were made to the system, many of these major changes which affected the appearance of things such as reports. Each passing day saw improvement in the attitude of doctors and nurses. In mid-1972, 66% of the doctors opposed the system. By the beginning of 1973, the majority of doctors, except for internists, favored the system. The El Camino system is perhaps one of the most thoroughly evaluated systems of any of the early development systems [20, 21]. The results of this evaluation did encourage further development in patient management systems.

The ultimate success of the system at El Camino led to the spread of this and other systems into other hospitals.

New crises were encountered as reduced funding from the federal government forced hospitals to decide if computerization was worth the cost and then to find the money to do it. Some hospitals were forced to abandon systems even though the systems finally looked promising.

Patient management systems tend to be primarily an automation of manual processes. In 1969, Feinstein [22] noted that while computers had been applied effectively in situations where a standard mechanism already exists for dealing with the data, computers had not yet had an

important impact on the more inherently clinical features of medical strategy and tactics. Many of the points made in this article are still valid criticisms of patient management systems. Schwartz [23] makes a similar point. He states that "few systems have fully explored the possibility that the computer as an intellectual tool can reshape the present system of health care, fundamentally alter the role of the physician, and profoundly change the nature of medical manpower recruitment and medical education - in short, the possibility that the health-care system by the year 2000 will be basically different from what it is today." We clearly have some distance to go.

The development of many of the components of a patient management system was driven in the late 1960s and early 1970s by interest in automated multiphasic health testing. The work of Dr. Morris Collen and his colleagues at the Kaiser-Permanente Medical Group in California [24,25] contributed to both a high level of interest in this field and in the progress of automation of tests, data collection and analysis. Dr. Collen stressed the need for AMHT systems to provide high quality testing, to provide good service to doctors and patients, and to be economical. In the early 1970s, only the first of these conditions had been met. The same could be said about other components of patient management systems.

Barnett, in an article [26] in The

New England Journal of Medicine, again argued the cause for computer applications in areas of medical care. He identified seven major areas in patient management systems which had made progress in development. Caceres [27] similarly reviewed the state of the art and stressed that the physician and patient care data must interact via the computer to realize automated patient management system goals.

Patient management systems, to be effective, do need to become a part of the physician/patient interface. Early systems were designed partly by the scientist, partly from the business world, and very little by the practicing physician. Systems designed in our computer laboratories often had major flaws which were obvious when we introduced them into the real world. Intelligent use of computers requires an understanding of the things computers do well: quantified information, well-defined vocabulary, great speed, repetition, accuracy, and versatile control. Humans, on the other hand, communicate by speech, vision, and touch, and have an unlimited vocabulary and great adaptability. It is when the computer is applied in areas of human incompetence, that previously impossible results can be achieved [28]. Too few systems take advantage of this fact. Often we fail to realize that the computer is no substitute for intelligence. It is not a magic box which can make gold from straw.

One early experience at Duke is

typical of the early days. For over two years, Duke had been involved with IBM in the development of a system called Clinical Decision Support Systems (CDSS). Duke had sent several MDs to work with IBM to develop a system in which the doctor would sit down with a computer terminal, describe the patient's history, physical findings, and laboratory data, and the computer would return the diagnosis and recommend a treatment. A remote system was set up at Duke, and the system was to be demonstrated to the faculty and house staff. Before the grand opening, a few doctors sat down and entered data on patient with some "easy" problems, such as influenza or pneumonia. After an hour of conversation with the computer, the computer was no closer to a conclusion than it was at the beginning. It seems that the computer did not know of the more common diseases since they were not well defined in the literature. The decision was made not to demonstrate or implement the system.

Instead, Duke then decided to develop a smaller subset of the system -- the automation of the initial or screening medical history. A 19-page mark sense form was designed to be completed by the patient, processed by the computer, and be presented to the doctor in narrative form. After three iterations, the form was complete, and actually did an effective job of collecting the initial medical history. Unfortunately, the logistics of processing this form on a large, remotely located main frame computer led to its

failure. The 19-page history was scanned by a mark sense reader and the results written on a 9-track magnetic tape. The patient's name, address, and free text data was keypunched onto cards, and the tape, cards, and program were submitted for delivery to the Triangle Universities Computation Center (TUCC), located some 12 miles away, for processing. Rarely did the tape, data, and program arrive at TUCC at the same time, and we spent most of our time trying to track down the components and get them together for processing. And when we managed that, the tape, created on one vendor's machine, could not be read on the other vendor's tape unit. The result was the history usually arrived in the doctor's hands a week after the patient had been seen. This problem was ultimately solved with a minicomputer directly interfaced to the scanner which produced the histories immediately.

We tried to use what we had learned with the automated histories to develop a computerized medical record for the Division of Obstetrics at Duke. We met with a group of physicians, argued over what parameters constituted an appropriate data base, and finally compromised by including any parameter any person felt they might use. The result was a 23 page, narrative printout for a new OB workup. Obviously, this computer program was not reducing the paper work nor helping the doctor. A quick redesign with the assistance of only one physician reduced the output to an acceptable amount; in fact, the essence of the output was

reduced to approximately ten lines on the first page in a starred box. We learned an important lesson - the difference between "what I might want and what I need".

Technology produced the minicomputer in the mid-60s and removed some of the problems associated with the mainframes. The cost of these computers was around \$30,000. The first of these was the LINC or Laboratory Instrumentation Computer developed at MIT and distributed to a number of system developers by NIH. This move by NIH was, in my opinion, one of the most significant events in the field of medical informatics, and really led to the development of the minicomputer industry. The LINC permitted an affordable, hands-on, real-time interaction with a computer. The minicomputer moved into the locations in which the projects were developed. The first minis were single user and had to be programmed in assembly language. The University of Washington in St. Louis developed a popular operating system which solved many of the system problems.

The minicomputer opened the door for many new development in patient management including clinical laboratory systems, automated ECG systems, and ambulatory care patient record systems. Octo Barnett, at Mass General, led the way with the development of COSTAR and the programming language MUMPS [29].

At Duke, we learned of the power of the minicomputer on a borrowed LINC-8 and designed a system in 1967 to create

on-line surface maps of cardiac body potentials - a process which had previously been performed on a mainframe at a much greater expense of time and money. A group of us then became interested in developing a computerized medical record. Our newly-acquired Digital Equipment Corporation PDP-12 was a dream. It had a 4K memory of 12-bit words, a CRT screen which had to be refreshed under program control, two 135 Kbyte DEC minitapes, 12 binary control switches, 6 A-to-D channels, and 6 potentiometers A-to-D inputs. Our first system was the Obstetrical Medical Record in which detailed data was retained during the pregnancy of some 1500 women who subsequently delivered at the Duke Medical Center. One tape would contain the records of approximately one month's pregnancies. Near the end of each month, someone was on call to change the tapes as the women came to Duke for delivery. The output was in upper case only on a teletype located just outside the delivery suite. One lesson we learned was that MDs did place value on the ability of a system to deliver information reliably as it was needed.

The programs were written originally in assembly language and used the LAP-6 operating system. These assembly language programs were later converted into a programming language called GEMISCH which we use today.

The PDP 12 gave way to a PDP 11/20 in the early '70s. The addition of a movable head, 1.2 Mbyte hard disk seemed to offer

more storage than we could ever need. This minicomputer had 28 Kwords of 16-bit memory. We wrote a multiuser operating system which supported 7 simultaneous users using a round-robin swapping algorithm.

User acceptance of computers played a major role in the development of patient management systems. The success of any innovation in a medical setting depends upon the attitude of the physicians involved. Surveys [30] indicated that physicians were reluctant to touch the keyboard of a CRT. They were doctors and "not typists". Systems designed and introduced by physicians were more apt to be accepted than one designed by a non-MD.

At Duke, we conducted one experiment which demonstrates this attitude. We asked a number of primary care physicians to look at a computer-generated medical history and a hand-written, human-generated history. The physicians overwhelmingly selected the hand-written form. We then reversed the process, taking the computer-generated medical history and copying it by hand, reformatting it slightly. We then took a human-generated history, typed it into the computer, and printed it on a drum printer so that it was obviously computer-generated. We showed these two histories to a number of physicians and again they overwhelmingly selected the hand-written form.

Many worried, and perhaps justly, that computers would be over-accepted, and

the computer's "word" would become truth. In an editorial in JAMA [31], M. Southgate compares today's physician with the medicine man of a primitive tribe who consults his spirits for knowledge. To the modern physician, the computer becomes the powerful and all knowing spirit.

Patients had little problem in accepting the computer as part of their health care delivery team [32]. Our own experience with using the PDP-12, certainly a rather imposing creature to a unenlightened patient, for collecting headache histories suggested that patients were less intimidated by the computer than the doctor. The adventuresome spirit of our patients was best illustrated by one incident involving a 67 year old lady. While answering questions about her headache, she would occasionally laugh. Not thinking our displays were humorous, we finally asked her what was funny. She replied that she was just waiting until the man hidden in the "computer box" would step out and greet her.

The developers of patient management systems were committed to the task. Typical of that attitude is Mel Hodge: "I am a believer. I happen to believe that the problems of health care delivery are susceptible to well-considered, well-executed approaches and that the introduction of information systems technology is among the more powerful approaches available. I have invested more than a decade to my life in this belief [8]." Many of us can now say we have invested a career to this belief.

Both of our speakers in this patient management systems section have contributed significantly to the development of this field. Both have been involved from the early years. Melville Hodge headed the development team which was responsible for the Technicon Medical Information System. This system was the first successful HIS which was subsequently implemented in a number of institutions and is today still a leader in the field of patient management systems.

Homer Warner, with his colleagues at the Latter Day Saints (LDS) Hospital in Salt Lake City, Utah, developed a number of subsystems over this period which constitute a patient management system called HELP.

The HELP system had its beginning in the late 1950s when Dr. Warner and colleagues began exploring the use of computers in the diagnosis of congenital heart disease [33]. The HELP system grew out of a group of subsystems which were designed to directly help the doctor or the nurse with specific data as relates to recognizing and dealing with specific events in a patient's illness [34]. These efforts included the goal of using the computer to enhance the decision making process [35] in the medical arena. Dr. Warner and colleagues dealt early with specific data collection, management [36], and analysis in such areas as the clinical laboratory, patient monitoring [37], and electrocardiographic interpretation by computer [38]. In the early 1970s, these

areas were integrated to use a common database. Warner describes the HELP system in a recent book [39].

The Technicon system, and the contributions of Hodge, is important because it was one of the first systems which worked and was accepted. This system primarily dealt with the service-related components of a patient management system - order entry and result reporting. Contributions were made in what was done and how it was done, even though other systems did not necessarily follow exactly the same patterns. The Technicon system represents one milestone in the development of patient management systems.

Warner and his group, through years of development, have added an important and necessary component of clinical involvement. By early on collecting data, Warner and his group were able to develop their own probabilities for diseases and their relationship to signs, symptoms, and findings. Most impressive is that the HELP system is still evolving at even now represents a state of the art approach to automated patient management.

These early years of development had to occur. I am always impressed that, as we became smart enough to recognize what we should do next, technology was always just available to enable us to do it. We are now entering a stage in which the tools seem to be adequate, the users seem to be receptive, the results justify the costs, and the applications seem to be useful. Perhaps we have now arrived at

the point in which computerized patient management systems can change the way we teach physicians, the way we practice medicine, and the way we do medical research.

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SOME ROOTS OF CLINICAL DECISION MAKING

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In early August, 1960 I received a telephone call from the Division of Research Grants, National Institutes of Health (NIH). The caller informed me that Dr. James A. Shannon, The Director of NIH, had decided to establish an Advisory Committee on Computers in Research and asked whether I would be interested in serving on the committee. Would I come to Bethesda, Maryland - the home of NIH - to discuss matters further? I replied that I would be glad to participate; since the early 1950s I had had an interest in the medical applications of computers.

On the first of several visits to NIH before the Advisory Committee on Computers in Research (ACCR) was activated, I found that the NIH Division of Research Grants (DRG) had been receiving research grant applications requesting funds for support of computer processing of data collected in basic research and clinical research projects. The peer review process of research grant applications was performed by members of NIH Study Sections and there were very few scientists who felt familiar enough with data processing and computer financial charges to evaluate the grant applications that requested funds

for a computer, or for computing time to support a particular type of research. Study Section members were often troubled by dollar amounts requested for computer related activities that seemed large compared with "reasonable" laboratory costs. The Division of Research Grants saw a problem developing and since DRG was responsible for processing the bulk of the research grant applications for all the National Institutes of Health they decided to review the situation with the NIH Director, Dr. Shannon.

Dr. Shannon, the imaginative and innovative director of NIH (1955-1968) presided over NIH during a period of rapid expansion and helped to build that organization into one of the strongest medical research organizations in the world. In that capacity he was a major force in the development of national policy and the mobilization of national resources for the support of biomedical research and research training. In my opinion he is responsible, in large part, for stimulating the growth of biomedical computing in the U.S. which enabled scientists and clinicians in the 1960s and 1970s to provide world wide leadership in the development of biomedical computing and computing-aids to medical diagnosis. Development that led to development of medical informatics.

By 1960 Dr. Shannon had spent quite a bit of time thinking about the possible contributions that automated computational

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devices could make to biomedical research. He had taken a one week intensive course on the operational capabilities of the "modern" computer at IBM Laboratories in Poughkeepsie, New York. About 1957 he suggested to the Scientific Directors of the NIH Institutes that they pool funds to supply NIH with a modern computational facility. His suggestion was rejected so out of the Director's office account he purchased an IBM 300 computer. On the national scene Dr. Shannon through NIH channels made an offer to approximately ten topnotch U.S. universities that NIH would purchase and support for five years a respectable computational facility within an adequate Biology Department, if courses in advanced mathematics and computational sciences would be made compulsory courses. The offer was informal and all of the universities refused the offer. The incident illustrates Dr. Shannon's foresight concerning the contributions to be made by computational science to the biological sciences.

These frustrations and the conviction that computers and computational science were important to biological sciences probably contributed to Dr. Shannon's decision to establish an Advisory Committee on Computers in Research. By the time DRG presented the grant application review to Dr. Shannon, he had a plan; he would establish NIH-ACCR.

On a second visit to NIH in early September, 1960, Dr. Dale R. Lindsay, assistant chief and later chief of the Division of Research Grants, Dr. Fay M. Hemphill, executive secretary of NIH-ACCR (1960-61) and later assistant chief, Division of Research Grants, reviewed details of an advisory committee operation and names of individuals to be invited to serve on the committee. I was asked to be Committee Chairman. I agreed readily. After a visit with Dr. Shannon to get his ideas concerning the Committee responsibilities, the first meeting of

NIH-ACCR was scheduled for September 20 and 21, 1960. Dr. Shannon would address the opening session of the Committee.

Meantime, staff members of the Division of Research Grants were in the final stages of committee organization. As a result of two earlier meetings, DRG staff had compiled a list of scientists who had used a computer in research projects or who were designing computers for medical applications.

The first meeting was an ad hoc panel of biomathematicians and biostatisticians convened by the NIH Division of General Medical Sciences at the National Institutes of Health on February 11, 1960. Dr. Frederick L. Stone, who was then assistant chief, Division of General Medical Sciences welcomed the group. Dr. Stone later became chief of GMS and played an important role with respect to NIH-ACCR activities. Stone pointed out that in the Report of the Senate Appropriations Committee in 1959 the U.S. Public Health Service the parent organization of NIH, was requested to provide some ideas and plans relative to the establishment of various types of central research facilities to universities (including medical schools) with special mention being made of clinical research centers (multi-purpose) and biomathematical centers. NIH-DGMS had been established in 1958 with the primary responsibility for providing the focus of support and interest in the basic medical sciences at NIH. The original charter of GMS mentions preclinical and clinical disciplines (not otherwise covered by the categorical NIH Institutes) -- along with basic biological and health related fields. The flexibility of the GMS charter enabled the Division to provide a large amount of monies to be committed for the development and support of biomedical computer activities.

The Ad hoc panel, chaired by Dr. John W. Fertig, Columbia University, concluded that all evidence placed medicine behind

fields of business and physical sciences in the use of computers. The panel agreed that more use could be made of computers and that manpower must be developed for "computer centers" and "biometrical institutes". The development of computing centers was thought to be an appropriate multiple agency undertaking. NIH-ACCR was later to take quite seriously the idea of "computing centers" and the Committee attempted to stimulate several university and hospital biomedical computing centers.

The second meeting, an ad hoc panel of consultants representing the National Science Foundation and the National Institutes of Health, was sponsored by the NIH Division of Research Grants and met at NIH on February 19, 1960. Dr. Richard Bolt, Associate Director of the National Science Foundation, (on leave of absence as chairman of the board of Bolt, Beranek and Newman, Inc.) chaired the meeting. Dr. Dale R. Lindsay, Assistant Chief and soon to be chief, DRG, opened the meeting. He suggested that the discussion of the group might be directed toward answering the following questions: 1) Have the life sciences reached the stage of sophistication which would primarily justify costly computer centers? 2) Should computer centers be established only in high density concentrations of scientists and should they be regional versus institutional? 3) Would the National Science Foundation program involve sufficient funds and scope to permit superposition of medical and biological needs upon centers they were already establishing?

In 1958 the National Science Foundation provided \$224,000 and in 1959, \$424,000 for computer use. NIH estimated \$250,000 in NIH funds had been provided for computer use in 1959. Most Committee members felt that requests for financial support of computer use would increase sharply in the near future.

To meet the computational needs the Committee developed the idea of computational centers. According to the minutes of

the meeting only brief mention was made of the small personal laboratory computer.

The Committee recommended that the review of grant applications as well as advising NIH on ways to meet the research needs, should be by a separate but overlapping committee of NIH choosing, but incorporating National Science Foundation consultants, to insure liaison and coordination. NIH-DRG staff now had the endorsement of an eminent group of scientists to organize a new review committee - soon to appear as NIH-ACCR.

Dr. Max A. Woodbury, mathematician from New York University and Dr. Otto H. Schmitt, biophysicist from University of Minnesota, were active participants in the February, 1960 ad hoc committee meetings and were subsequently helpful and influential members of NIH-ACCR.

At the first meeting of the NIH Advisory Committee on Computers in Research, September 20, 1960, Dr. Shannon welcomed the Committee members and outlined the Committee responsibilities for 1) studying the needs of computers in medical and related biological research and advising him as to the proper role the National Institutes of Health should play in the support of computer centers and of other research involving the use of computers; 2) reviewing applications for research grants involving computer adaptation or utilization and making recommendations to the NIH Advisory Councils; and 3) surveying as scientific leaders the status of research in this general field in order to point out areas in which research activities should be initiated or expanded.

Dr. Shannon encouraged the members of NIH-ACCR to plan broadly, and to look to long range gains for medical research through the use of computers. He assumed that as individuals we would encourage and stimulate activities in the broad field he had outlined.

So the NIH-ACCR was assigned dual duties first, as an advisory group to the Director

of NIH, on problems related to bio-medical information processing and to "stimulate activity" in the biomedical computing field; and second, as a reviewing body to adjudge the formal grant applications related to biomedical information processing. Ordinarily the programming or stimulation activity is separated from the evaluation of grant applications but Dr. Shannon felt that the computer field required that both activities be assigned to a single committee.

The dual duties of the Committee were to cause problems later when grant applications "stimulated" by ACCR members were presented to the entire ACCR for evaluation. The dual duties however lasted throughout the three year lifetime of NIH-ACCR. In January, 1964 the Committee was renamed the Computer Research Study Section and the dual duties were dropped. The Study Section was to emphasize grant evaluation.

After the opening remarks by Dr. Shannon at the September 20, 1960 meeting, the Committee members were introduced and I was introduced as the Committee Chairman. I felt some uneasiness about being in this position because I did not know the majority of the Committee members and this was my first experience with an NIH extramural grant review committee. NIH intramural activities were somewhat more familiar as a result of my two years (1956-57) of active duty in the Public Health Service as a radiologist in the Department of Radiology, Clinical Center, National Institutes of Health. It was during this two year assignment that I first met Dr. Shannon.

My anxieties about Committee operation were considerably alleviated by Dr. Fay Hemphill, Chief, Statistical Design and Analysis Section, NIH-DRG, who had agreed to be Executive Secretary of ACCR. Fay knew NIH procedures and personnel. He was a great help to me personally and to ACCR. He was Executive Secretary 1960-61 and Dr. Bruce D. Waxman was Executive Sec-

retary 1961-63. Bruce continued the excellent help to the Committee. Later when I found myself or the Committee in difficulty two individuals were available with wise counsel and advice Dr. Dale R. Lindsay, Chief, NIH-DRG, and Dr. Frederick L. Stone, Chief, NIH Division of General Medical Sciences (later the National Institute of General Medical Sciences).

The majority of ACCR members did not know each other so there was no "old buddy" feeling about the group in the early days. Members had been selected for their expertise in some aspect of biomedical or computer science but no one person could claim to be an expert in the field of biomedical computing. The Committee members decided, I think wisely, to spend some time getting acquainted and educating each other. The original ACCR members whose Committee tenures were staggered according to NIH tradition were: William R. Adey, M.D., (UCLA); Paul Armer (Rand Corporation); Mary A. B. Brazier, D.Sc. (MIT and later UCLA); David Garfinkel, Ph.D. (University of Pennsylvania); Alston S. Householder, Ph.D. (Oak Ridge National Laboratory); William N. Papiian, M.S. (Lincoln Laboratory-MIT); George A. Sacher, Jr., B.S. (Argonne National Laboratory); Joseph E. Schenthal, M.D. (Tulane University); Otto H. Schmitt, Ph.D. (University of Minnesota); Normal Z. Shapiro, Ph.D. (NIH); Ralph W. Stacey, Ph.D. (University of Ohio); Max A. Woodbury, Ph.D. (New York University); Lee B. Lusted M.D., Chairman, (University of Rochester).

Members who joined the Committee later were Scott Adams, B.L.S.; Robert C. F. Bartels, Ph.D.; Julian Bigelow; Jerome R. Cox, Jr., Sc.D.; Gordon K. Moe, Ph.D., M.D.; Alan Perlis, Ph.D.; James M. Sakoda, Ph.D.; Allen Scher, Ph.D.; Homer R. Warner, M.D. Ph.D.; and Consultant George S. Malindzak, Jr., Ph.D. Committee members posed for a portrait in 1962.

This group of talented individuals took seriously the original charge from



NIH ADVISORY COMMITTEE ON COMPUTERS IN RESEARCH - MAY 1962

Seated Left to Right: Mary A. B. Brazier, W. Ross Adey, Otto Schmitt, Ralph W. Stacy, Joseph E. Schenthal, William N. Papian, James M. Sakoda and Homer R. Warner.

Standing Left to Right: Fay M. Hemphill, George S. Malindzak, Jr., Rose S. Doying, George A. Sacher, Jr., Max A. Woodbury, Lee B. Lusted, Alston S. Householder, Bruce D. Waxman, Scott Adams and David Garfinkel.

The Director, NIH, that its responsibility should include "stimulating activities" with a very broad view of the problems of biomedical computing.

Committee members accompanied NIH staff members on numerous "stimulation visits" to universities, medical schools and hospitals throughout the country to discuss local problems dealing with biomedical computing and to determine how NIH could help the investigators or institutions with their needs. In the early phases of the NIH-ACCR activity, these visits were very helpful; the suggestion to many investigators that they make use of a small "Planning" grant proved particularly worth while.

Committee members felt that they needed to develop their own abilities and wisdom concerning the field of biomedical computing through the use of workshops, symposia and use of consultants. Two special ses-

sions were held for the purposes of educating Committee members and planning Committee activities.

The first special meeting, a "Workshop on Biomedical Computing", was organized and directed by Dr. Ralph W. Stacy. The meeting was held at Ohio State University July 3-13, 1961. The workshop gave Committee members an intense 10 day exposure to information about the current state of biomedical computing in the United States and provided time to consider what guidelines might be proposed to The Director, NIH, for the national support of biomedical computing. The second special meeting of NIH-ACCR was held at Massachusetts Institutes of Technology's Lincoln Laboratory, Lexington, MA. on November 15 and 16, 1961. Lincoln Laboratory was a large laboratory facility operated for the U.S. Air Force by MIT. Computer development at Lincoln Laboratory had been impressive

with computers such as average response computer ARC-1, TX-0, TX-2 and RX-1. The TX-2, with the possible exception of the IBM Stretch, was at that time the most powerful computer in operation for biological modeling and laboratory data processing. There was also a really small, inexpensive "general purpose" computer called "LINC" being developed at the Lincoln Laboratory and the Committee members wanted to see LINC in operation.

At the November, 1961 meeting the Committee worked on the topics of biomedical computing centers, financing of data processing equipment, medical and health services automation, and special problems related to the development of biomedical computing equipment. A "Guidelines" report was prepared for The Director, NIH, as a result of the meeting.

A demonstration of the LINC computer was given for Committee members by Mr. Wesley A. Clark. The demonstration of LINC was received with enthusiasm and the Committee urged further development of LINC. The first time that the LINC was presented at a scientific meeting was at the "Conference on Special Aspects of Electronic and Computer-Assisted Studies of Bio-Medical Problems", Washington D.C., September 14-16, 1961. The Conference was co-sponsored by NIH-ACCR and chaired by Dr. Otto H. Schmitt. A number of NIH-ACCR members participated in the discussions. One of the questions pertinent to NIH-ACCR interests was; what features would characterize a widely useful electronic computer specially designed to serve the needs of research in the life sciences?

As a part of the discussion of this topic, Mr. Wesley A. Clark discussed the LINC (Laboratory Instrument Computer) which had been designed at Lincoln Laboratory. The event is noteworthy because LINC is a unique contribution to biomedical data processing. The development of LINC and the subsequent manner in which it was introduced for use among biomedical researchers

is an historical landmark.

The Committee supported the continued development and evaluation of LINC and appended the history of LINC development to the Final Report to the Director, NIH, entitled "Guidelines For The National Institutes of Health Support of Biomedical Computing" by the Advisory Committee on Computers In Research, December, 1963. I have reproduced Appendix B with the LINC history from that report and attached it at the end of this article.

The story of LINC is a success story and it is said that success has many fathers. Several years ago there was a symposium at the National Institutes of Health celebrating the 20th anniversary of LINC. Many persons and organizations were recognized which contributed to the success of the LINC program. In reporting the proceedings of the LINC anniversary, The NIH Record, January 3, 1984, said, "Perhaps equally important, the LINC program demonstrated that resourcefulness and imaginative Federal management could influence the course of both science and industry."

It is gratifying to think that NIH-ACCR played a small role in this successful enterprise.

In the early 1960s there was evidence of increasing acceptance of the role of computers in biomedical research by this country's biomedical research scientists and evidence of what was the beginning of a major transition from traditional methods toward a truly quantitative and theoretical biology.

Congress was in a mood to increase the funds of NIH. The Eighty-Seventh Congress of the United States approved five million dollars in the Fiscal Year 1962 budget of the NIH Division of General Medical Sciences for the support of regional biomedical computer centers and instrumentation centers. Consideration must be given to the interest and encouragement of Senators Lister Hill and Hubert Humphrey,

Representative John Fogarty and Mrs. Mary Lasker, health-care activist and philanthropist.

The Committee was much concerned about the shortage of personnel in this country who were knowledgeable at the interface between bioscience and computer science. The Committee urged that NIH now concentrate some attention on training programs at this interface through NIH Training programs and Fellowships. Later, in commenting on the Committee report, Dr. Shannon said that he would emphasize training to a greater degree than the Committee recommended.

During the September, 1960 through December 31, 1963 lifetime of NIH-ACCR the Committee held ten regularly scheduled meetings, reviewed 307 grant applications and site visited about 60% of these applications. A total of 178 applications were finally approved and paid for a total first year commitment of \$17,873,263 (as of December 1963). The future years' commitments on these applications totaled \$23,081,114 which gives a total for all years of \$40,954,377. In 1987 this amount of monies does not seem surprising but in the early 1960s it represented a substantial commitment by NIH to the development of a national biomedical computing capability.

In closing this brief review of NIH-ACCR activities, I think it is interesting to look at the types of computers primarily engaged in life sciences research in the early 1960s. Table 1 shows the installation by state and is reproduced from the NIH-ACCR Final Report of The Director, NIH, December, 1963. A copy of Table 1 is appended to this report.

I have given the preceding time and space to tell a little of the NIH-ACCR story because the joint effort of ACCR and NIH gave great impetus to biomedical computing and indirectly to quantitative biomedical sciences. I have not seen the NIH-ACCR activities described elsewhere.

The "stimulation" activities and the grant review, site visits offered unusual opportunities for the Committee members to meet a large number of scientists who were working in a variety of disciplines. My long time interdisciplinary interests in computer-aids to medical diagnosis and in medical decision making were stimulated by several of the professional contacts I made during NIH-ACCR trips.

Next, I recount some events and activities that influenced my work on computer aids to medical diagnosis and medical decision making.

During my college years from 1939 to 1943 World War II was in progress and accelerated programs were advised for men students, particularly, if one were a science major and draft eligible. My majors were mathematics and physics. Scientists were in great demand during the World War II period both by the military services and the U.S. Government civilian research agencies, such as the Office of Scientific Research and Development. With the help of my mathematics professor at Cornell College who had left college teaching for a research position at Harvard University and Leo L. Beranek, a Cornell College graduate, who was an acoustics engineer at Harvard, I obtained a position as research associate at the Radio Research Laboratory (RRL), Harvard University. RRL was operated by Harvard University under a contract with Division 15, Office of Scientific Research and Development. The director of the laboratory was Dr. Frederick Terman, on leave of absence from the engineering school at Stanford University. The purpose of the laboratory was to do research and development on techniques and equipment to "jam" enemy radar, i.e., to confuse enemy radar so that the target could not be identified. I was assigned to work on electronic airborne jammers. This equipment was to be carried by bombers or fighter planes and was to confuse the enemy radar used to direct

antiaircraft artillery.

I had no training in electronics or engineering principles but with night school classes and tutoring at the work bench I quickly learned the basics of electronic engineering. My electronics experiences during the 1943-1946 period served as the basis for later medical electronic, biomedical engineering and computer engineering interests. Interdepartmental seminars were held regularly at RRL and at one of the seminars I heard a discussion of signal detection theory in the context of defining the requirements to "see" a radar signal against a noisy background. Later these discussions were to come to mind as I was developing the use of receiver operating characteristic (ROC) analysis of radiologic images in the context of medical decision making.

When World War II ended many of us who had worked as civilian engineers were undecided about what to do -- get a job in industry, go to graduate school, or change career path. Most of us had been deferred from military duty and still had service requirements facing us. In addition to my physical science and engineering interests, biology and psychology had been in the back of my mind as areas ripe for application of physical science principles. Interdisciplinary programs were very rare in the mid 1940s so I decided that medical school offered the most likely path to develop my interests.

My application to Harvard Medical School was accepted in December, 1945, and in the Fall of 1946, I began medical school. A Biophysical Laboratory had been organized about this time by Dr. A. K. Solomon and in the summer between my first and second years in medical school, I worked on instrumentation projects for Dr. Solomon. Drs. Dewitt and Marney Stetten had set up their laboratories in the Biophysical Laboratory area and I helped Dr. Dewitt (Hans) with some instrumentation. By the time I was assigned to NIH in 1956 the Stettens

had moved to NIH and I renewed our friendship.

During the summer between the second and third medical school years I applied for a position with the U.S. Public Health Service to work on a Heart Disease Control Program in Newton, Massachusetts. The position offered a reserve commission in the U.S. Public Health Service and guaranteed that a medical student could finish medical school before being called to active duty. Since I was still eligible for military service having been a civilian scientist during the war, I saw this as a way to assure medical school graduation. The decision was fortuitous because it resulted in my Public Health Service active duty at NIH ten years later.

Harvard Medical School students could choose clinical assignment at the various teaching hospitals associated with Harvard. My favorite was Massachusetts General Hospital (MGH) for medicine, surgery and radiology rotations. The experiences at MGH as a medical student were not to be forgotten in 1961 and 1962 when I worked to "stimulate" a computing center at MGH on behalf NIH-ACCR.

Interdisciplinary programs for biomedical, physical and engineering science were not yet satisfactory in my opinion in 1951 so I decided to pursue my interests in the specialty of radiology. My advisor, Dr. Shields Warren, a pathologist, who had made an extensive study of tissue damage resulting from radiation exposure, advised me to apply for a residency with Dr. Robert Stone, Chairman of the Radiology Department at University of California San Francisco.

The years 1951-1956 in San Francisco were spent learning radiology, pursuing some medical electronic interests and renewing my friendship with Dr. Jerre D. Noe at Stanford Research Institute in Palo Alto, California. Jerre and I had worked together in England in 1944 and 1945 at the American British Laboratory

in Great Malvern. American British Laboratory was the name given to the overseas branch of the Harvard Radio Research Laboratory. Jerre was the leader of a group of engineers assigned to a variety of projects. My projects included supervision of the installation of radar frequency receiver equipment in P-38 fighter aircraft to be flown over enemy V-1 and V-2 missile launching sites to determine whether the missiles were radio or radar guided (they were not so guided); and supervising the reassembly and testing of a captured enemy gun-directing radar (FuSe62). The radar contained some circuits for calculating target distance but did not have what we would call computer elements.

After the war ended Jerre Noe returned to Stanford University to obtain a Ph.D. in electronics and in the early 1950s was the engineer in charge of a project at Stanford Research Institute to build a large computer for the Bank of America. The computer called ERMA (Electronic Record Machine Accounting) was the first large computing system made specifically for banking procedures. On weekends I would visit Jerre to watch ERMA grow and we would talk about the possibility that a computer like ERMA could process patient's medical records in hospitals and help physicians with medical diagnosis. There was concern expressed in medical journals that a knowledge explosion was enveloping the field of medicine and there was speculation that computers could be used to help solve some of the problems. I felt that medical data could be processed by computer and that medical information could be made more useful to physicians by repackaging it in a more usable form. I wasn't sure how this could be done but the idea of making information more useful by making it more usable stuck with me.

The Stanford University-Palo Alto environs in the early 1950s was showing signs of an electronics boom. William R.

Hewlett, president of Hewlett-Packard Corporation in Palo Alto, was national president of the Institute of Radio Engineers (IRE, now called the Institute of Electrical and Electronic Engineers) in 1954; Dr. Frederick Terman, who had directed Harvard's Radio Research Laboratory during World War II had returned to Stanford University and was Provost of the University. The first chapter of the IRE Professional Group on Medical Electronics was established in Palo Alto and I was an active participant. (IRE Professional Groups were started as special interest groups within the IRE Society.) It was through these activities that I kept in touch with developments in the electronic and computing fields.

I had planned a career in academic radiology and intended to stay at University of California, San Francisco, until I received a letter on August 3, 1955, from the regional medical director of the U.S. Public Health Service located in San Francisco. The letter informed me that my Inactive Reserve Commission would expire shortly and asked whether I wished to be reappointed. If I dropped the commission I would be subject to the "Doctor Draft" and if I continued the Public Health Service Commission I would be required to serve two years active duty. The choice seemed obvious - select two years with Public Health Service. After several lengthy discussions with PHS Division of Personnel I was assigned to the Department of Radiology, Clinical Center, National Institutes of Health for duty, January, 1956.

The Radiology Department at the NIH Clinical Center was fairly new. It had been designed by Dr. Henry Kaplan who had left to take the Radiology Chairmanship at Stanford Medical School and the department head was Dr. Theodore Hilbish when I arrived. The department provided the commonly requested radiographic studies but emphasized cardiovascular radiol-

ogy because of the strong leadership of Dr. A. Glenn Morrow, Chief of the Clinic of Surgery and Dr. Eugene Braunwald, Chief of Cardiology Branch, National Heart Institute.

The daily work schedule of fluoroscopic examination reporting was fairly light and I was left with time to explore other NIH opportunities. The NIH library provided excellent opportunities for browsing, a pastime I have always enjoyed, among a large collection of books and journals. I renewed my acquaintance with Dr. Dewitt Stetten and paid frequent visits to the laboratory of Dr. Robert L. Bowman, who was Chief of the Laboratory of Technical Development in the National Heart Institute. I had met Dr. Bowman through the activities of the IRE Professional Group on Medical Electronics. On one of my visits to Dr. Bowman's laboratory he told me he was on his way to see Dr. Shannon to discuss an instrumentation problem and that I might accompany him. And so I met Dr. Shannon. In later visits I had opportunities to tell Dr. Shannon about my interests in electronic instrumentation and electronic computers.

Early in 1956 an opportunity arose to do consulting work for Airborne Instruments Laboratory (AIL), Mineola, Long Island, New York. The president of AIL was John Dyer, an engineer who had been in charge of the research and development group I joined at Harvard Research Laboratory in 1943. AIL had organized a department of medical and biological physics, headed by Walter E. Tolles, and I was invited to act as a consultant on the general application of electronic methods to medicine. AIL had obtained a contract from the NIH National Cancer Institute to develop an instrument to be used in the mass screening of cytological smears for the detection of cervical cancer. At that time the cytological smear, when used according to the technique established by Papanicolaou, had become the most important method for the

early detection of cancer of the cervix, but there were not enough people trained to screen the smears. The instrumentation problems seemed challenging and I requested permission from the Public Health Service to act as a consultant on medical electronics. My request, to my pleasant surprise, progressed rapidly up through the administrative hierarchy to the Chief, PHS Division of Personnel, and returned promptly approved and initialled by all parties including The Director, NIH.

The consulting activities at AIL had two fortuitous outcomes. The first was a series of events that led to meeting Robert S. Ledley. We subsequently collaborated on studies of mathematical and implemental aids to medical diagnosis. The second outcome came as a result of discussions about criteria to be used for performance evaluation of the cytological smear screening instrumentation. Ideas developed at that time led me later to introduce Receiver Operating Characteristic (ROC) analysis for medical image observer performance and medical decision making. I will recount the story of work with Ledley first and discuss ROC analysis later.

William J. Horvath, Ph.D., was assistant head of the AIL medical and biological physics department and it was his responsibility to evaluate the performance of the Cytoanalyzer, the experimental instrument designed to screen the cytological smears. On several occasions Horvath and I discussed my interests in providing computer aids for medical diagnosis. Horvath said he had heard a paper presented at a meeting of the Operations Research Society by a young dentist named Robert Ledley on the topic of logical aid to medical diagnosis and he thought an article had been published subsequently. (R.S. Ledley, Logical Aid to Symptomatic Medical Diagnosis. Operations Research, Vol 3, August, 1955). He thought Ledley could be located at the National Bureau of

Standards in Washington D.C. and he suggested I contact him. With several telephone calls I did locate Ledley, we had a short chat and agreed to meet in my office at the NIH Clinical Center.

We found that we had been thinking about similar problems and possible solutions. The problems were caused by the large and increasing volume of medical literature. The possible solutions involved mathematical and computational aids for the physician. Ledley had obtained a degree in dentistry and subsequently had done work in mathematics and physics receiving a masters degree in mathematics. I can remember some brisk discussions. Ledley knew more mathematics and computer science than I did and I knew more clinical medicine. Eventually we proposed mathematical techniques and the associated use of computers as an aid to the physician in diagnosis and treatment selection. In an article published in *Science* in 1959 with the provocative title, "Reasoning Foundations of Medical Diagnosis" (*Science* 130:9-21, July 3, 1959) we suggested that symbolic logic, probability and value theory aid our understanding of how physicians reason.

The article was a medical "best seller" in terms of the number of reprints requested and the number of citations by other authors subsequently. Before the days of abundant copying machines one criterion of the success of an article was the number of requests for a reprint of the article received by the authors. Requests for the "Reasoning Foundations" article ran into the thousands. Exactly how many requests were received is uncertain since both Ledley and I sent out reprints. I remember a request which came from a science teacher at the Bronx (New York) High School of Science asking for a large number of reprints to be used in mathematics and science classes. The article was promptly translated into Russian and appeared in a monograph published in Moscow in 1961.

There were outspoken critics of the ar-

ticle and most of the criticisms seemed to be directed at our proposal that Bayes' theorem be used. Some commentators said, "Doctors don't think Bayes" - We never said they did. Some critics pointed out the inapplicability of Bayes' theorem to medical diagnosis because patient signs, symptoms and laboratory tests are not independent and the diagnoses being considered are not mutually exclusive.

The "Reasoning Foundations" article pitched me into at least three areas of controversy, some of which persist to the present day. The first involved the appropriateness and acceptability to the medical profession of computer-aided medical diagnosis; the second involved the appropriate use of Bayes' theorem in computer-aided medical diagnosis; and the third led into the struggle between two schools of thought about statistical inference; the Bayesian school and the classical school. I was thoroughly unprepared for the third controversy. The Bayesian position appealed to me and I worked hard to understand what the controversy was about.

Bayes' theorem is an uncontroversial consequence of the definition of conditional probability and the fact that probabilities sum to 1. If probabilities describe orderly opinions, Bayes' theorem describes how such opinions should be revised in the light of new information.

In the early 1960s physician-investigators who wished to use Bayes' theorem were often discouraged by a consultant who was often a classical statistician. Ward Edwards, an early-on and still active Bayesian, influenced my thinking greatly by his writings and helped me in various ways to develop the field of medical decision making. He commented recently, (von Winterfeldt D, Edwards W: *Decision Analysis and Behavioral Research*. Cambridge, Cambridge University Press, 1986, pp 161), "When the Bayesian point of view became visible in the 1960s, most Bayesians were convinced that in time classical null hypothesis

testing, would die out. The Bayesians of the 1960s clearly underestimated the power of human inertia. More important, perhaps, they underestimated the difficulty of making a transition from one form of statistical inference to another."

Despite the difficulties, interest in the use of Bayes' theorem was evident in the early 1960s and continues to the present time. Very few clinical investigators were able to test the applicability of Bayes' theorem to computer-aided diagnosis because they didn't have good data in readily usable form. Two investigators who did were Dr. Homer R. Warner and Dr. Gwilym S. Lodwick.

I met Dr. Warner at a meeting of the NIH National Heart Institute Training Grant Directors at Dearborn Inn, Dearborn, Michigan, June 3-4, 1960. I gave a talk on biomedical computing and discussed the use of Bayes' theorem. Dr. Warner said he had access to a Burroughs 205 digital computer and had good data on the signs, symptoms and electrocardiographic findings in a group of patients with congenital heart disease. He would try Bayes' theorem. He reported his results on the diagnosis of congenital heart disease from clinical data with a digital computer at the American Heart Association Meeting, St. Louis, Missouri, October 21-23, 1960 and subsequently published what I believe to be the first article which used a set of clinical data to demonstrate the applicability of Bayes' theorem (A Mathematical Approach to Medical Diagnosis. Application to Congenital Heart Disease. JAMA 177,177-183, July 22, 1961). Warner and colleagues at Latter-day Saints Hospital, Salt Lake City, Utah, expanded and improved the early computer activity to attain a hospital information system that provides decision-support programs for clinicians. (The HELP System. J Med Syst 7: 87-102, 1983).

Dr. Lodwick, Chairman, Department of Radiology, University of Missouri had collected data on a large series of primary

bone tumors and showed that he could predict the histologic diagnosis of each case from examination of the roentgenogram. His average rate of accuracy in predicting the correct histologic diagnosis was 80 percent. I heard about Dr. Lodwick's data on a trip about 1959 to the University of Missouri to work with Dr. Theodore E. Keats on an "Atlas of Roentgenographic Measurements". I was always on the lookout for good clinical data to test the use of Bayes' theorem. Dr. Lodwick readily agreed to develop a research program for a probabilistic approach to the diagnosis of bone tumors. Lodwick submitted a grant application that was processed by NIH-ACCR - I believe it was the first research grant from a radiologist that the Committee recommended for approval. The grant CA-06263, "Computer Analysis of Tumor Roentgenograms" was active for 17 years, an excellent record. An early publication by Lodwick and colleagues (Computer Diagnosis of Primary Bone Tumors. A Preliminary Report. Radiology 80:273-275, 1963) reported that the computer program using Bayes' theorem and Lodwick's roentgenographic criteria could predict the correct histologic diagnosis in 77.9 percent of the cases. Predictive accuracy improved with more experience. Lodwick's work did a great deal to stimulate interest in computer-aided analysis of radiographic images and I think helped to raise the level of awareness about possible uses of computers in medical care. During my visits to the University of Missouri I met Dr. Donald A. B. Lindberg, a member of the Department of Pathology. We discussed possible uses of computers in pathology and I told him about Dr. Baldwin Lamson, a pathologist at UCLA Medical Center and his interests. Dr. Lindberg subsequently became director of the University of Missouri Medical Center Computer Program and made significant contributions to computer usage in pathology and to the development of the general

field of medical informatics.

Drs. Warner, Lodwick and Lindberg are members of a very small group of individuals who have made significant contributions to the biomedical computational field from the early 1960s for a period of twenty-five years or more. Many individuals have made shorter and less prolonged contributions, very few have stuck to the subject for a significant length of time.

Meanwhile, whatever happened to Bayes' theorem and the problems of conditional nonindependence of medical data? Ledley and I investigated the problems caused by nonindependence of patient attributes (signs, symptoms, laboratory data, etc.) during the 1959-1963 period with a grant from NIH (RG-7844, Mathematical and Implemental Aids to Medical Diagnosis) using data from patients with proven lung cancer. We found that clusters of attributes could be formed and those could be treated as new conditionally independent attributes even though the attributes within the clusters were not independent. I don't think we published on the subject. Warner was careful not to include in the list of symptoms any two symptoms which invariably occurred together in a patient with congenital heart disease and he grouped certain mutually exclusive symptoms which required special handling.

Several investigators continued to investigate the limitations of mutually exclusive diagnostic outcomes and attribute dependency. One who pursued the subject was Dennis G. Fryback at the University of Michigan. I met Fryback in the early 1960s at a Bayesian Research Conference organized by Ward Edwards at the University of Michigan. The Bayesian Research Conferences started in 1962 - the 25th Anniversary Conference was in 1987 - were a focus for medical decision making discussions and provided important undergirding for the latter formation of the Society For Medical Decision Making. Fryback's work (Bayes' Theorem and Conditional Nonindependence

of Data in Medical Diagnosis. Computers and Biomedical Research 11:423-423, 1978) demonstrated that the greater the number of variables used in the Bayesian calculation, the more the degradation of the model's performance when the data violate conditional independence.

The Bayesian computer-assisted medical decision making systems of Dr. F. T. de Dombal and associates deserve special attention. Some time in the late 1960s or early 1970s I met de Dombal at an international meeting -- probably in London. He had read about Bayes' theorem and was interested in developing a computer system to aid in the diagnosis of abdominal pain. de Dombal is a surgeon at St. James's Hospital in Leeds, England and abdominal pain is a common problem seen in hospital emergency room patients. de Dombal did develop a Bayesian computer-aided diagnostic system that was more accurate than the physicians' diagnosis of abdominal pain. If the computer diagnostic recommendations had been followed, fewer "unnecessary" appendectomies would have been performed and fewer patients with actual appendicitis would have been delayed in receiving appropriate surgery (Computer-aided Diagnosis of Acute Abdominal Pain. Br Med J 2:9-13, 1972). de Dombal was also concerned about whether the computer-aided diagnostic system would be transferable to a variety of clinical and geographic settings. Through a series of experiments he has shown that system is transferable (Zoltie N, Horrocks J, de Dombal FT: Computer Assisted Diagnosis of Dyspepsia - Report of Transferability of a System, With Emphasis on Early Diagnosis of Gastric Cancer. Meth Inform Med 16:89-92, 1977). The Bayesian system for the diagnosis of acute abdominal pain runs on microcomputers and is being used extensively in British emergency departments. The United States Naval Submarine Force has adapted de Dombal's Bayesian diagnostic programs for use by medical

corpsmen aboard submarines to help in the evaluation of abdominal pain, chest pain and psychiatric disturbances. (A computer Based Diagnostic/Information Patient Management System for Isolated Environment. MEDIC Ten Years Later. Bernard L. Ryack, U.S. Naval Submarine Medical Research Laboratory. Report No. 1089. 4 February 1987). Preliminary discussions with U.S. National Aeronautics and Space Administration (NASA) have been started to explore the applicability of the computer-assisted diagnostic systems for orbiting space stations.

If "Doctors Don't Think Bayes' Theorem", what do they think about in doing patient diagnoses and management? Many attempts have been made to answer this question and studies of physicians' clinical reasoning have provided important roots for the field of clinical decision making. Although medical educators and clinicians have given attention to diagnostic reasoning I wish to emphasize the work of cognitive psychologists who have focussed on the information processing approach to cognition. This approach aims to characterize the underlying thought processes by recording and analyzing the verbalizations of persons as they attempt to solve problems. The focus is on explaining human thinking in terms of basic psychological elements and principles. (Elstein AS and colleagues. Medical Problem Solving. An Analysis of Clinical Reasoning. Cambridge, Massachusetts. Harvard University Press, 1978).

Elstein and other investigators have suggested that physicians' diagnostic reasoning is a hypothetico-deductive inference process in which the physician is involved in a sequential hypothesize-and-test process. The physician conceptually constructs a "model" of the patient. It is interesting to note that the psychological studies of problem solving by medical experts have been influential in current medical artificial intelligence (AI) research (Shortliffe EH. Computer Programs to Support Clinical Decision Making. JAMA 258:

61-66, 1987).

My interests in Bayesian and information-processing approaches to medical diagnosis were combined in a project I undertook for the American College of Radiology in 1971. There had been allegations that for some types of x-ray examinations between 10 and 30 percent of the examinations were "wasted" i.e., they did not contribute useful information for diagnosis or treatment of a patient. The American College of Radiology (ACR) decided to study the problem. An ACR Committee on Efficacy Studies was appointed which I chaired. We undertook a study of the use of x-ray examinations in hospital emergency rooms.

The ACR Committee on Efficacy Studies had to develop definitions of efficacy and to determine how to measure the efficacy of diagnostic procedures. It was decided and I think the idea was proposed by Ward Edwards, that a hierarchical approach to efficacy be defined. This was the first time that levels of diagnostic test efficacy had been defined and tested. The efficacy levels would be called efficacy-1, efficacy-2, and efficacy-3. They were defined as follows.

Efficacy-3 can be thought of as ultimate outcome efficacy to the patient. Ex post, an x-ray procedure is efficacious-3 for an individual patient to the extent that the patient is better off as a result of the performance of the procedure than he would have been if the procedure had not been performed.

Efficacy-2, which can be called patient management efficacy is less long range in outlook. It concentrates on the use of diagnostic information. Ex post, a procedure has efficacy-2 to the extent that physicians are led to treatment outcomes as a result of the procedure that differ from the actions that would have been taken in the absence of the diagnostic procedure.

Efficacy-1 refers to the information

content of the procedure, regardless of whether or not the information content had an effect on subsequent management. In this sense, a diagnostic procedure is efficacious-1 to the extent that physicians are led to change their thinking about the nature of patients' conditions by the information provided by the procedure.

During 1972 and 1973 Drs. Ward Edwards, Dennis Fryback and radiologist, Dr. John Thornbury conducted a pretest of procedures for the measurement of efficacy including data collection forms at the University of Michigan. As a consequence of physician response problems that were found in the pretest, the ACR Efficacy Study decided to concentrate on Efficacy-1.

The operational definition of Efficacy-1 comes directly from Bayes' theorem that may be expressed in a particularly simple form: final odds equals initial odds times likelihood ratio or $FO = IO \times LR$ where LR stands for "likelihood ratio". The likelihood ratio for a diagnosis given certain diagnostic information is defined as the ratio of two conditional probabilities, the probability of the diagnostic information given the truth of the diagnosis and the probability of the diagnostic information given the falsity of the diagnosis.

The likelihood ratio LR is the precise assessment of how the diagnostic information from an x-ray procedure (or laboratory test) transforms the initial odds IO to final odds FO. We adopted the likelihood ratio as the efficacy-1 measure for x-ray procedures. An undiagnostic or inefficient x-ray procedure would have a likelihood ratio of 1. The more the likelihood ratio deviates from 1 the more efficacious the procedure is in terms of Efficacy-1.

Emergency room physicians, after some training in the use of probability and odds, were asked to judge initial odds or probabilities of a diagnosis before an x-ray examination was obtained and corresponding final odds or probabilities after the x-ray examination had been completed

and the physician knew the result. We calculated the likelihood ratio to obtain the efficacy-1 of the examination.

A total of 381 emergency room physicians and 52 radiologists provided approximately 14 judgments of initial and final odds or probabilities each; the study included 8658 protocols. The seven x-ray procedures studied (skull, cervical spine, chest, abdomen, lumbar spine, extremities and intravenous pyelogram) together account for approximately 90 percent of all radiographs taken in emergency rooms.

We found that physicians were able to judge odds or probabilities with a high degree of consistency and a reasonable degree of calibration. Physicians tended to overestimate probabilities attached to abnormal diagnoses.

For the seven x-ray procedures we found a total of 4 percent inefficient procedures as defined by Efficacy-1 and found that about 6 percent of the procedures were requested primarily for medical-legal reasons. The project ended with recommendations for future studies of Efficacy-2. (Lusted LB. A Study of The Efficacy of Diagnostic Radiologic Procedures. Final Report on Diagnostic Efficacy to Dr. Gerald Rosenthal, Director, National Center For Health Services Research, Health Resources Administration, DHEW. 31 May 1977). (See also Winterfeldt and Edwards. Decision Analysis and Behavioral Research. Cambridge, Cambridge University Press. 1986. Chapter 5, pp 448-452.).

In an interesting extension of the American College of Radiology Efficacy Study, Dr. Eugene L. Saenger and colleagues demonstrated Efficacy-1 and Efficacy-2 for nuclear medicine lung scans in patients suspected of having a pulmonary embolism. The study and analyses which were sponsored by the Society of Nuclear Medicine Committee on Public Health and Efficacy compared two methods to evaluate efficacy, namely, Logistic regression and entropy minimax pattern detection. The study showed that

lung scan findings had a significant influence on the physician's diagnostic thinking and that no combination of patient signs and symptoms was found which would predict reliably, a priori, which patients had pulmonary emboli. (Saenger EL, Buncher CR, Specker BL, McDevitt R. Determination of Clinical Efficacy: Nuclear Medicine as Applied To Lung Scanning. J Nucl Med 26: 793-806, 1985. Gift DA, Schonbein WR, Saenger EL, Potchen EJ: Application of an Information-Theoretic Method of Efficacy Assessment. J Nucl Med 26:807-811, 1985).

Efficacy studies of diagnostic tests including laboratory tests and imaging procedures and the efficacy assessment of new medical technologies continue to be high priority areas of research.

Before proceeding I want to recount stories of two NIH-ACCR "stimulation" activities in which I was involved. Both have had favorable long term outcomes.

The first incident occurred at a "stimulation" talk I gave on biomedical computing for the San Francisco County Medical Society on January 18, 1962. I mentioned that NIH was interested in receiving grant applications requesting funds for biomedical computation projects. After the meeting Dr. Morris F. Collen introduced himself and said that he had been developing a multiphasic screening and diagnosis program for California Kaiser-Permanente in San Francisco Bay Area. He said the multiphasic screening data could use computer processing and he would like to know more about NIH grant funding. I put him in touch with Dr. Homer Warner, a member of NIH-ACCR, to work out a grant application. Dr. Collen has been a pioneer and a major medical information systems builder (Collen MF et al: Automated Multiphasic Screening and Diagnosis. Am J Publ Hlth 54, 741, 1964). Lindberg has published an interesting account of the Kaiser Permanente medical information system in his book, "The Growth of Medical Information Systems in the United States". Lexington, Massachu-

setts, Lexington Books, 1979, pp 62-63; 70-71.

The second activity involved a series of events whose purpose was to stimulate the development of a computation center at Massachusetts General Hospital. Earlier in this article I wrote that during my medical school experience I had several clinical clerkships at MGH. I have also noted that as a member of the NIH-ACCR I took seriously the challenge to develop biomedical computation centers in universities and hospitals. I decided that MGH would be an excellent site for a computation center and I set out to see what could be done. I visited Dr. John Knowles, the General Director of MGH, in late 1961 or early 1962. Dr. Knowles was interested in developing a computer system for patient information management that would include clinical data, medical record data and financial data but he pointed out that he did not have knowledgeable persons on his staff. How could we get started? I knew from conversations with my friend, Leo L. Beranek, President, Bolt, Beranek and Newman, Inc. (BBN, a consulting firm in Cambridge, Massachusetts) that BBN had computer scientists and computers available. Perhaps BBN could help MGH. Beranek found that a member of BBN staff, Jordan J. Baruch, was eager to work with MGH. Dr. Knowles assigned members of his staff to work with Baruch and discussions continued from 1962 into 1963 when I think Baruch submitted an application to NIH for funds to develop a computational facility for MGH. I think all of us involved in the planning, and that very much included Dr. Knowles, recognized that MGH should develop "in house" computer equipment and staff competence as quickly as possible.

Fortunately, the individual to lead the MGH development appeared in the person of Dr. G. Octo Barnett. I have heard that Octo was recruited for the position by Dr. Robert Ebert, who was then Dean of Harvard Medical School and had been chief of medi-

cine at MGH. Dr. Barnett has been the first and to 1987, the only director of the MGH Laboratory of Computer Science. Dr. Barnett and his group have been very productive in a variety of medical computational and decision making areas. (Barnett GO and colleagues. DXplain. An Evolving Diagnostic Decision-Support System. JAMA 258:67-74, 1987. See also Lindberg DAB: The Growth of Medical Information Systems in the United States. Lexington, Massachusetts, Lexington Books, 1979, pp 40-42).

I return now to some recollections of the introduction of Receiver Operating Characteristic (ROC) analysis to medical decision making and events associated with writing the book, Introduction To Medical Decision Making. (Lusted LB. Introduction To Medical Decision Making. Springfield, Illinois. Charles C. Thomas, 1968).

In the summer of 1962, I left the Department of Radiology at the University of Rochester for a position that combined radiology at University of Oregon and a directorship of the automatic data processing program and computation facility at the Oregon Regional Primate Research Center. The computational facility included a Scientific Data Systems model 920 computer with 8,192 words (24 binary bits/word) of random access memory. The machine could do 60,000 additions per second and was probably the first such computer to be used solely for experiments in biomedical recording keeping and biomathematical modeling. Max Palevsky, President, Scientific Data Systems, came to visit us several times to see the applications of the SDS920 computer.

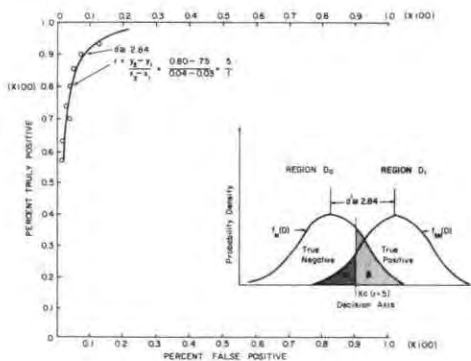
The position provided me with a respite from an active clinical radiology schedule and it was during this time, 1962-1968 that I worked out the application of ROC analysis to medicine and wrote a book on medical decision making. By March, 1965, we had a computer-based medical record system in full operation at the Oregon Regional Primate Center. Robert Coffin and I re-

counted experiences with the system in the book PRIME (Primate Information Management Experiment) (Lusted LB, Coffin RW: PRIME. An Automated Information System For Hospitals and Biomedical Research Laboratories. Chicago, Illinois. Year Book Medical Publishers, 1967). Walter Stahl and I had studied several conceptual models of medical diagnosis and had experimented with Turing Programming on the SDS920 computer as a promising method for stimulating the mixed logical processes and algorithms which occur in a medical diagnosis problem. (Lusted LB, Stahl WR: Conceptual Models of Diagnosis. [In] The Diagnostic Process. Proc of a Conference at the University of Michigan, May 9-11, 1963. Ed. John A. Jacques, April, 1964. pp 157-180).

Receiver operating characteristic analysis is now generally recognized as the most appropriate methodology for evaluating the diagnostic performance of medical imaging procedures and ROC curves are used to compare the performance of laboratory tests. ROC analysis is derived from the theory of signal detection based on the theory of simple dichotomy. The research and applications of signal detectability had been in the fields of engineering and psychophysics since the days of World War II but the importance of these developments had not filtered into medicine by the late 1950s and early 1960s.

Through an interesting set of circumstances which I have recounted in a recent editorial, I was able to introduce the concepts of ROC analysis to medicine (Lusted LB. ROC Recollected. Med Decis Making 4: 131-135, 1984). Briefly, the significant events were: hearing about signal detection theory at Harvard Radio Research Laboratory in 1944 or 1945 in the context of an observer seeing a radar signal against a noisy background; participating in a study of "observer variation" for the detection of pulmonary tuberculosis by chest x-ray examination (1945); preparing a performance curve from the data of the tuberculosis

study to try to explain observer variation (see illustration) with the substantial help of William Horvath at Airborne Instruments Laboratory, 1957 (Lusted LB. Logical Analysis in Roentgen Diagnosis. Radiology 74:178-193, 1960); reading in 1965 a book on signal detection edited by Swets (Signal Detection and Recognition by Human Observers. New York, Wiley, 1964) and reading a book in 1966 by Green and Swets (Green DM and Swets JA. Signal Detection Theory and Psychophysics. New York, Wiley, 1966) and observing that the observer performance curve from the tuberculosis chest film study was an operating characteristic curve that closely matched ROC curves shown in the two books on signal detection theory.



Operating characteristic curve for the interpretation of chest photofluorograms for the presence of pulmonary tuberculosis (Fig. 42, pp 123 in Lusted, Introduction to Medical Decision Making, 1968)

After observing that the performance curve for the tuberculosis chest film study had a similar shape to an ROC curve that might result from an auditory or visual signal detection experiment in psychophysics, the questions in my mind were; Could a disease process such as tuberculosis result in a "signal" as seen on a chest x-ray film? In signal detection theory terms, could a normal population of persons be compared to a "noise distribution" and an abnormal population containing the disease to be detected be compared to a

"signal plus noise distribution?" If "yes" was the answer to the questions then medical science and clinical medicine would have statistical decision theory and ROC methodology to tackle a host of problems such as observer variation and observer performance, evaluation of diagnostic test and imaging procedures and comparison of the performance of diagnostic procedures including cost/benefit analysis comparison. I concluded that the answer was "yes" to both questions and I said so in a 1967 lecture. (Lusted LB. Introduction to Medical Decision Making. Digest of the 7th International Conference on Medical and Biological Engineering. Stockholm, 1967. p 297). However, it was not until 1971 that work with colleagues Charles Metz and David Goode-nough at the University of Chicago provided the experimental studies to demonstrate the great generality of medicine of the ideas concerning signal detection and ROC analysis with which signal detectability theorists had been working. (Lusted LB. Decision Making Studies in Patient Management. N Eng J Med 284:416-424, 1971).

I do not wish to pursue the basics of ROC analysis. An excellent primer has been provided by Metz (Metz CE. Basic Principles of ROC Analysis. Sem Nucl Med 8:283-298, 1978) and more recently Metz has reviewed the status of ROC methodology and summarized ROC analysis in diagnostic radiology and radionuclide imaging (Metz CE. ROC Methodology in Radiologic Imaging. Invest Radiol 21:720-733, 1986).

By the Fall of 1967 I had finished a draft of the book, "Introduction To Medical Decision Making". ROC analysis was included as an important procedure to be used in medical decision making studies and with the substantial help of Ward Edwards a translation of signal detectability theory into more general Bayesian language was provided (Introduction To Medical Decision Making pp 128-132). I believe this was the first published material which provided a table of equivalent terms for Bayes' formulae and

signal detectability formulae. We demonstrated an isomorphism between Bayesian decision theory and the signal detection-psychophysics approach. Particular attention was given to the use of the likelihood ratio L because of the difference in emphasis placed on L by the two schools of thought.

In Bayesian terms the decision maker does not base his decision on a critical likelihood ratio L_c , where L_c is the critical likelihood ratio just adequate to transform initial odds into final odds; $FO = L_c IO$. He bases his decision on his final opinion, which is controlled both by his initial opinion and by the observations he has made. It is the final opinion that controls the decision after all observations have been completed.

The reader will remember that we adopted this strategy in the American College Radiology Efficacy Study. We asked the physician to judge the initial odds IO and the final odds FO . We calculated the likelihood ratio LR_c .

Signal detection theorists were particularly interested in giving an account of the process of observing as separated from the decision process to which the observations are an input. Therefore, they preferred to partition the decision problem in a way that emphasizes the critical likelihood ratio, L_c .

An ROC graph does emphasize the likelihood ratio since the curve is generated by a series of points each of which is a likelihood ratio. The curve represents all of the possible combinations of true positive fractions (TPF on Y-axis) and false positive fractions (FPF on X-axis), which describe the inherent detection performance of an observer or the detection characteristic of a diagnostic test.

The likelihood ratio is $L = \frac{TPF}{FPF}$. L_c , the critical likelihood ratio is calculated from the costs and benefits associated with the true and false decision outcomes.

We have now reached the chronological

point to recognize the emergence of decision analysis and to note the significant effect which it had on clinical decision analysis and medical decision making. The period from 1963 to 1971 was clearly the time when decision analysis emerged as a viable activity. I have borrowed extensively from the interesting account of decision analysis history by von Winterfeldt and Edwards (Decision Analysis and Behavioral Research, pp 566-569). Decision analysis seems to have occurred at Harvard, Stanford and University of Michigan as a result of groups led by Howard Raiffa, Ronald A. Howard and Ward Edwards. In 1968, Raiffa published a fairly small paperback book called "Decision Analysis", which contained relatively implementable treatments of decision strategies including cost-benefit and cost-effectiveness strategies. Though Raiffa did not coin the term "decision analysis" (R. A. Howard did that), Raiffa's 1968 book gave the topic much visibility and academic interest. A large number of medical articles and the book, "Clinical Decision Analysis" (Weinstein MC, Fineberg HV. Clinical Decision Analysis. Philadelphia, W B Saunders, 1980) testify to Raiffa's influence.

Although I had read some of the articles by Howard and had heard of decision analysis I did not mention the term in my book, Introduction To Medical Decision Making, which appeared in 1968, the same year as Raiffa's book. By the mid 1970s the number of medical journal articles and scientific papers presented at meetings indicated that a few individuals appreciated the potential medical contributions of decision sciences supported by computer information processing. My friend and colleague, Dr. Eugene L. Saenger at the University of Cincinnati, reminded me that the time was ripe to focus the diverse medical decision making interests by organizing a society and that we should do so promptly. I was still involved with the American College of Radiology Efficacy Study and I

was not very enthusiastic about organizing a society. Saenger persisted and I am glad that he did. A one day meeting entitled, Decision Making in Diagnostic Medicine, was sponsored by The Society of Nuclear Medicine and held in Atlanta, Georgia, January 25, 1967. The chairperson was Barbara J. McNeil, M.D., Ph.D., Harvard Medical School. A panel discussion on "Problems in Translating These Concepts (of decision making) into Medical Practice" chaired by Henry N. Wagner, Jr., M.D., The Johns Hopkins Medical Institution, plus informal conversations convinced me that Saenger's timing was right and that we should make plans for a Society For Medical Decision Making. I thought the Society should have a journal and that the Society and the journal should be started simultaneously. Saenger took on the responsibility for the Society and I worked on the journal. The Society For Medical Decision Making was officially chartered under the laws of the State of Ohio and the first annual meeting, largely organized by Saenger was held at the University of Cincinnati in September, 1979.

Starting the journal, Medical Decision Making, took a bit longer. Volume I appeared in 1981. I was editor-in-chief for the first five volumes of the journal during the period 1981-1985. Many individuals contributed to the early success of the Society and the journal. The help of Harvey V. Fineberg, M.D., Ph.D., Harvard School of Public Health and Stephen G. Pauker, M.D., Tufts-New England Medical Center deserves special recognition.

Several years ago Dr. J. Robert Beck, Dartmouth-Hitchcock Medical Center, suggested to me that it would be interesting to do a study of the literature of medical decision making using the techniques of citation analysis. The study was motivated by a desire to identify the most highly influential early references in two research fronts of medical decision making; computer-assisted diagnosis and clinical

decision analysis. The objective of the study was to compile a core reference list for teaching. The technique of citation analysis was chosen to develop a manageable historiography of these research fields.

The study appealed to me; particularly because Beck and Kathryn I. Pyle, A.M.L.S., a medical librarian at Dartmouth would do most of the work. The study produced results which are presented as an evolutionary tree of the field of medical decision making, 1959-1982; and as such, seems appropriate to conclude this article.

(Beck JR, Pyle KI, Lusted LB. A Citation Analysis of the Field of Medical Decision Making, 1959-1982. Computer-Aided Diagnosis and Clinical Decision Analysis. Med Decis Making 4:449-468, 1984).

Citation indexing was developed by Garfield as an aid to the compilation of bibliographies. Before the publication of the "Science Citation Index" (SCI), one could only perform bibliographic studies backward in time. With the advent of citation indexing, forward literature searching became possible. Each annual volume of SCI is organized by cited article and contains a list of publications which have cited the specific early work in that year.

A concept derived from citation indexing is cocitation frequency. In cocitation analysis, pairs of articles are studied for the links between them. Cocitation strength is a metric of the relative importance and linkage of two primary documents. As such, it is suitable for various multivariate analyses. We used multivariate procedures that included a hierarchical clustered analysis. The output of the procedures was a set of graphs each depicting the 2-space representation of the relationship among a set of articles over a time interval. The placement of the articles on the plot reflected their global cocitations; clustered articles were circled together.

The final analysis of the study was the development of the historical tree of the

fields of computer-aided diagnosis and clinical decision making. To build this tree a simple rule was devised; each document was connected to the most recent core article it cited.

The literature of medical decision making, beginning with Ledley and Lusted's 1959 article in *Science* was studied. From five experts in the fields of computer-aided diagnosis and clinical decision analysis and from a review of *Index Medicus* subject headings, a list of 56 articles and five books was compiled and analyzed. These core documents are shown at the end of this section. Three time periods were selected for analysis; 1961-1970, 1971-1975, and 1976-1980. Cocitation maps for 1961-1970 and 1976-1980 are shown in Figures 1 and 2 at the end of this section.

The letter-number combination on the cocitation map refers to an article on the core document list. For example, in Figure 1, L59 identifies the Ledley, Lusted 1959 article in *Science*, W61 identifies Warner and colleagues' 1961 article in *JA MA*. These two articles are the oldest documents in the core list. Cluster analysis also identified Warner and colleagues' 1964 paper on Bayesian analysis of congenital heart disease (W64), and Boyle and associates' 1966 paper from the *Quarterly Journal of Medicine* on computer-aided diagnosis of goiter (B66) as bibliographically related to the two early papers. Two articles from *The Lancet* in 1967, from Hall (H67) and Scadding (S67), were also cited together frequently up to 1970.

In the period 1976 - 80, 61 articles and books were analyzed. Figure 2 shows the relationships among the 15 most frequently cocited (minimum ten between two documents) articles and books from the core list over the final five-year period. The two early articles Ledley 59 and Warner 61, are once more clustered, with cocitation of Lusted's 1968 monograph (L68). Galen and Gambino's book (G75) "Beyond Normality", is recognized as bibliographically

related to Vecchio's 1966 article on predictive value (V66). There is a large cluster of leading articles on clinical decision making, with the greatest cocitation frequency over the 1976-80 period being between Schwartz 73 (S73) and McNeil's 75 "Primer" (M75). Other articles in this cluster include Gorry and associates' companion piece in the *American Journal of Medicine* 1973 (G73), Raiffa's 1968 textbook on decision analysis (R68), two articles by Pauker in 1975 and 1976 (P75, P76), and Kassirer's 1976 (K76), "The Principals of Clinical Decision Making. An Introduction to Decision Analysis", from the *Yale Journal of Biology and Medicine*. As time passes, the principal effect of the cocitation analysis is to show a merging of clustered articles.

An evolutionary tree of the field of medical decision making, 1959-1978 is shown in Figure 3. By means of a tree diagram linking documents by citations, the central evolution including roots, trunk and tree branches of the fields computer-assisted diagnosis and clinical decision analysis is portrayed. Pre-1971 articles that did not cite other documents in the list (i.e., articles in the original set of 36 documents that graduated in the final list) are included, connected to future documents that cited them. Documents are connected by a simple rule, the most recent publication on the core list cited. For example, Feinstein 73 (F73) cites no articles after Scheff's 1963 (S63) article on decision rules in *Behavioral Science*.

Figure 3 shows four general areas of scholarship, among which there is some overlap. In the left center is the early work in computer-assisted diagnosis and Bayesian reasoning, flowing from Warner 61 (W61). Hall 67 (H67) quotes Vecchio 66 (V66), a paper that had no citation to early core documents, but achieved a progressively wider exposure over time.

Above and further to the left, de Dombal 72 (D72) cites Ledley and Lusted (L59)

and continues the computer-aided diagnosis stream of scholarship. In this latter section of computer-assisted diagnosis papers, several come from the field of laboratory medicine.

The right central section begins with Lusted 71 (71), which borrows from Collens' 1970 article (C70) on cost-effectiveness of multiphasic screening and quotes Goërry 68 (G68). The Lusted 1971 (L71) article appeared in The New England Journal of Medicine and spawned the field of clinical decision analysis as shown above and to the right of L71 in Figure 3. I attribute the influence of this article in large part to the fact that it was published in The New England Journal of Medicine, a journal widely recognized for the influential role it plays. The New England Journal of Medicine gave the medical decision making field a tremendous boost when the editor, Dr. Franz J. Ingelfinger, devoted the entire issue on July 31, 1975, to decision making in medicine; the first time The New England Journal had ever devoted an entire issue to a single topic. Barbara McNeil's "Primer" (M75) appeared in that New England Journal issue and the branches from M75 would be numerous if we had structured the tree beyond 1978.

At the far right of Figure 3 is Feinstein's work (F73,74,77), three articles in the 1970s connected to the early literature (S63 and L59).

We have reached a favorable stopping point in the exploration of the tree of computer-aided diagnosis, clinical decision analysis and medical decision making. It remains for me to thank the many individuals who have participated in this exploration and contributed to its success.

CITATION ANALYSIS OF MEDICAL DECISION MAKING

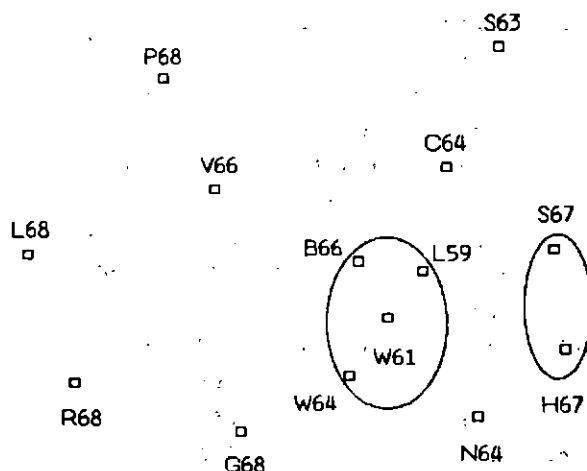


Figure 1. Cocitation map, 1961-1970. In Figures 1,2 and 3, documents are identified by the first author initial and year of publication (e.g., L59: Ledley 59). The documents are listed following Figure 3. The cluster of four articles in the center of the figure (Ledley 59, Warner 61, Warner 64, Boyle 66) represent early review articles and papers in computer-aided diagnosis. Note that distances on this graph represent strength of association, but because of scaling can only be treated as approximate. (Figure 2, from Beck, Pyle and Lusted).

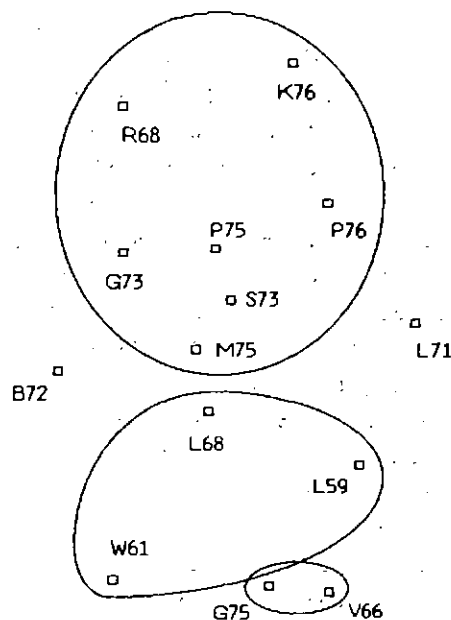


Figure 2: High-frequency cocitation map 1976-1980. Only the top 15 articles, in terms of cocitation between 1976 and 1980 are graphed. The large upper cluster represents the early general work in clinical decision analysis. (Figure 4, from Beck, Pyle and Lusted).

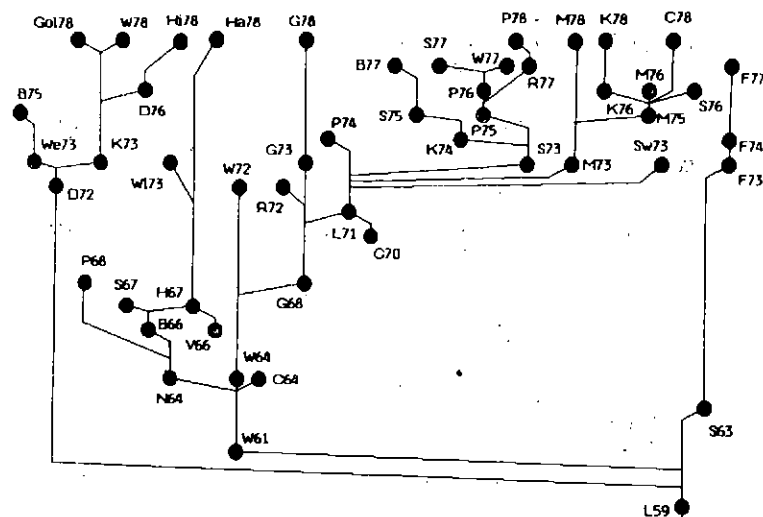


Figure 3. Evolutionary tree of the field of medical decision making, 1959-1978. Only journal articles are shown in this tree. Solid lines represent direct citation in later works of earlier papers in the tree. (Figure 5, from Beck, Pyle and Lusted).

Appendix: Computer-Aided Diagnosis and Clinical Decision Analysis. Core Document List, 1959-78

Authors	Title	Journal	Year
Ledley RS Lusted LB	Reasoning foundations of medical diagnosis	Science	1959
Warner HR Toronto AF Veasey LG	A mathematical approach to medical diagnosis	JAMA	1961
Stephenson R Scheff TJ	Decision rules, types of error and their consequence in medical diagnosis	Behav Sci	1963
Collen MF Rubin L Neyman J Dantzig GB Baer RM Siegelau AB	Automated multiphasic screening and diagnosis	Am J Public Health	1964
Nugent CA Warner HR Dunn JT Tyler FH	Probability theory in the diagnosis of Cushing's syndrome	J Clin Endocrinol Metab	1964
Warner HR Toronto AF Veasey LG	Experience with Bayes' theorem for computer diagnosis of congenital heart disease	Ann NY Acad Sci	1964
Boyle JA Greig WR Franklin DA Harden RMCG Buchanan WW McGin EM	Construction of a model for computer-assisted diagnosis. Application to the problem of non-toxic goitre	Q J Med	1966
Vecchio TJ	Predictive value of a single diagnostic test in unselected populations	N Engl J Med	1966
Hall GH	The clinical application of Bayes' theorem	Lancet	1967
Scadding JG	Diagnosis. The clinician and the computer	Lancet	1967

Gorry GA Barnett GO	Sequential diagnosis by computer	JAMA	1968
Lusted LB	Introduction to Medical Decision Making. Springfield, Illinois: Charles C. Thomas		1968
Pipberber HV Klingeman JD Cosma J	Computer evaluation of statistical properties of clinical information in the differential diagnosis of chest pain	Methods Inf Med	1968
Raiffa H	Decision Analysis. Introductory Lectures on Choices Under Uncertainty. Reading, Massachusetts: Addison-Wesley		1968
Cornfield J	The Bayesian outlook and its application	Biometrics	1969
Collen MF Feldman R Siegefaub AB Crawford D	Dollar cost per positive test for automated multiphasic screening	N Engl J Med	1970
Lusted LB	Decision-making studies in patient management	N Engl J Med	1971
Barnoon S Wolfe H	Measuring the Effectiveness of Medical Decisions. An Operational Research Approach. Springfield, Illinois: Charles C. Thomas		1972
De Dombal FT Leaper DJ Staniland JR McCann AP Horrocks JC	Computer-aided diagnosis of acute abdominal pain	Br Med J	1972
Reece RL Hobbie RK	Computer evaluation of chemistry values. A reporting and diagnostic aid	Am J Clin Pathol	1972
Warner HR Olmsted CM Rutherford BD	HELP. A program for medical decision-making	Comput Biomed Res	1972
Feinstein AR	An analysis of diagnostic reasoning. I. The domains and disorders of clinical microbiology	Yale J Biol Med	1973
Gorry GA Kassirer JP Essig A Schwartz WB	Decision analysis as the basis for computer-aided management of acute renal failure	Am J Med	1973
Knill-Jones RP Stern RB Girmes DH Maxwell JD Thompson RP Williams R	Use of sequential Bayesian model in diagnosis of jaundice by computer	Br Med J	1973
Metz CE Goodenough DJ Rossman K	Evaluation of receiver operating characteristic curve data in terms of information theory, with applications in radiography	Radiology	1973
Schwartz WB Gorry GA Kassirer JP Essig A	Decision analysis and clinical judgment	Am J Med	1973
Swets JA	The relative operating characteristic in psychology	Science	1973
Werner M Brooks SH Wette R	Strategy for cost-effective laboratory testing	Hum Pathol	1973
Winkel P	Patterns and clusters. Multivariate approach for interpreting clinical chemistry results.	Clin Chem	1973

Feinstein AR	An analysis of diagnostic reasoning. III. The construction of clinical algorithms	Yale J Biol Med	1974
Katz MA	A probability graph describing the predictive value of a highly sensitive diagnostic test	N Engl J Med	1974
Patrick EA Stelmack FP Shen LYL	Review of pattern-recognition in medical diagnosis and consulting relative to a new system model	IEEE Syst Man Cybern	1974
Blomberg DJ Kimber WD Burke MD	Creatine kinase isoenzymes. Predictive value in the early diagnosis of acute myocardial infarction	Am J Med	1975
Galen RS Gambino SR	Beyond Normality. The Predictive Value and Efficiency of Medical Diagnoses. New York: Wiley		1975
McNeil BJ Keeler E Adelstein SJ	Primer on certain elements of medical decision making	N Engl J Med	1975
McNeil BJ Varady PD Burrows BA Adelstein SJ	Measures of clinical efficacy. Cost-effectiveness calculations in the diagnosis and treatment of hypertensive renovascular disease	N Engl J Med	1975
Pauker SG Kassirer JP	Therapeutic decision making. A cost-benefit analysis	N Engl J Med	1975
Sunderman, FW	Current concepts of "normal values," "reference values," and "discrimination values" in clinical chemistry	Clin Chem	1975
Dawid AP	Properties of diagnostic data distributions	Biometrics	1976
Kassirer JP	The principles of clinical decision making. An introduction to decision analysis	Yale J Biol Med	1976
McNeil BJ Adelstein SJ	Determining the value of diagnostic and screening tests	J Nucl Med	1976
Pauker SG	Coronary artery surgery. The use of decision analysis	Ann Intern Med	1976
Sisson JC Schoemaker EB Ross JC	Clinical decision analysis. The hazard of using additional data	JAMA	1976
Büttner J	Die Beurteilung des diagnostischen Wertes klinisch-chemischer Untersuchungen	J Clin Chem Clin Biochem	1977
Feinstein AR	Clinical biostatistics XXXIX. The haze of Bayes, the aerial palaces of decision analysis, the computerized Ouija board	Clin Pharmacol	1977
Rifkin RD Hood WB Jr	Bayesian analysis of electrocardiographic exercise stress testing	N Engl J Med	1977
Safran C Desforbes JF Tsichlis PN Bluming AZ	Diagnostic planning using computer assisted decision-making for patients with Hodgkin's disease	Cancer	1977
Tompkins RK Burnes DC Cable WE	An analysis of the cost-effectiveness of pharyngitis management and acute rheumatic fever prevention	Ann Intern Med	1977
Weinstein MC Stason WB	Foundations of cost-effectiveness analysis for health and medical practices	N Engl J Med	1978
Casscells W Schoenberger A Grayboys TB	Interpretation by physicians of clinical laboratory results	N Engl J Med	1978

Elstein AS Shulman LS Sprafka SA	Medical Problem Solving. An Analysis of Clinical Reasoning. Cambridge, Massachusetts: Harvard University Press		1978
Fryback DG	Bayes' theorem and conditional nonindependence of data in medical diagnosis	Comput Biomed Res	1978
Goldberg DM Ellis G	Mathematical and computer-assisted procedures in the diagnosis of liver and biliary tract disorders	Adv Clin Chem	1978
Gorry GA Pauker SG Schwartz WB	The diagnostic importance of the normal finding	N Engl J Med	1978
Habbema JD Hilden J Bjerregaard B	The measurement of performance in probabilistic diagnosis. I. The problem, descriptive tools, and measures based on classification matrices	Methods Inf Med	1978
Hilden J Habbema JD Bjerregaard B	The measurement of performance in probabilistic diagnosis. III. Methods based on continuous functions of the diagnostic probabilities	Methods Inf Med	1978
Kassirer JP Pauker SG	Should diagnostic testing be regulated?	N Engl J Med	1978
Metz CE	Basic principles of ROC analysis	Semin Nucl Med	1978
Patton DD	Introduction to clinical decision-making	Semin Nucl Med	1978
Wardle A Wardle L	Computer aided diagnosis. A review of research	Methods Inf Med	1978

From the "Final Report to the Director, NIH" by the
NIH-ACCR, December 1963.

APPENDIX B

The history of the LINC (Laboratory Instrument Computer) development goes back to 1957 when Mr. Wesley A. Clark designed the Average Response Computer (ARC-1) at Lincoln Laboratory-MIT. The ARC-1 was used in studies of electroencephalograms and was found to be a useful research instrument. About this same time another Lincoln Laboratory Computer, the TX-0, was being used to analyze EEG patterns. From this computer-aided EEG research experience Mr. Clark concluded that it would be helpful for biological researchers to have a stored program type of computer which would be somewhere between an ARC-1 and TX-0 in size. The design for a stored program type of machine, subsequently called LINC, was worked out by Clark and Lt. Charles E. Molnar, AFCRL. They stated that "In designing the LINC, the principal underlying objective has been to maximize the degree of control over the instrument by the individual researcher. Only in this way, it is felt, can the power of the computer be usefully employed without compromising scientific objectives.

In 1960, Clark and Molnar (working in the group directed by Mr. William N. Papian at Lincoln Laboratory-MIT) began the actual design and construction of a laboratory type, general purpose digital computer, the goal being a machine which would

- (1) be small enough in scale so that the individual research worker or small laboratory group could assume complete responsibility for all aspects of administration, operation, programming and maintenance;

From the "Final Report to the Director, NIH" by the NIH-ACCR, December 1963.

- (2) provide direct, simple, effective means whereby the experimenter could control the machine from its console, with immediate displays of data and results for viewing or photographing;
- (3) be fast enough for simple data processing "on line" while the experiment is in progress, and logically powerful enough to permit later, more complex calculations if required;
- (4) be flexible enough in physical arrangement and electrical characteristics to permit convenient interconnection with a variety of other laboratory apparatus, both analog and digital, such as amplifiers, timers, transducers, plotters, special digital equipment, etc. while minimizing the need for complex intermediating devices;
- (5) include features of design which facilitate the training of persons unfamiliar with the use of digital computers.

The name LINC was coined sometime during 1961 and it was used to describe the laboratory-type, general purpose digital computer at both the ACCR "Workshop on Biomedical Computing" in July, 1961, and at the NSF-Sponsored "Research Training Conference in Computer Techniques for Biological Scientists" at MIT in the summer of 1961.

During late 1961 and early 1962 word about LINC spread rapidly in the scientific community. Interest among researchers was so favorable that in the latter part of 1962 discussions were held with representatives of NIH and NASA* and, as a result, NIH Contract PH43-63-540 was drawn up to support a LINC Evaluation Program. The contract required the selection of scientific advisory committee to be charged with (1) choosing participants for the LINC Evaluation Program, (2) monitoring the progress of the program and (3) making a final evaluation of the program. The evaluation would ascertain how well the LINC meets the five design objectives listed above, and determine its mechanical and electronic reliability in prolonged laboratory usage. More generally, the evaluation program hopes to determine whether the use of digital computers in the biomedical laboratory significantly advances the acquisition of knowledge.

The LINC Evaluation Board accepted the proposal that the most efficient procedure for providing appropriate background training would be to have each biological scientist participating in the Evaluation Program assemble his own LINC from prefabricated components. During each of two "assembly" phases, July 1-25 (6 participants) and August 5-30, 1963 (6 participants), the participants were given lectures on programming, operation and maintenance of LINC. How the LINC development group finally managed to assemble the needed components by July, 1963, and how the class teaching was organized is another interesting story. However, the fact remains that all 12 LINC's were assembled and each participating scientist did learn how to program and maintain his LINC. These LINC's, plus 9 others, are now in operation in as many different biomedical research laboratories distributed around the country.

The LINC Evaluation Program continues through 1964 and 1965 but one important point has already been proven by the LINC training program. The summer program in 1963 demonstrated that it is possible, with proper planning and execution, for biologists to learn a great deal of computer technology in a very short time.

From the "Final Report to the Director, NIH" by the
NIH-ACCR, December 1963.

TABLE I

COMPUTER INSTALLATIONS PRIMARILY ENGAGED IN LIFE SCIENCES RESEARCH, 1964

State and Institution	Type of Computer
<u>ALABAMA</u>	
Alabama, University of	IBM 1620
<u>CALIFORNIA</u>	
Camarillo State Hospital	IBM 1440
California, University of, Davis	IBM 7040* - IBM 1710*
California, University of, Los Angeles	IBM 7094 - IBM 1410 - CDC 160A
California, University of, San Francisco	IBM 1410
Pacific State Hospital	G-15
Southern California, University of	IBM 1710
Stanford University	LINC (2)
<u>COLORADO</u>	
Colorado, University of, Medical Center	CDC 160A
<u>DISTRICT OF COLUMBIA (Washington)</u>	
Georgetown University	IBM 1620*
<u>FLORIDA</u>	
Miami, University of	IBM 1401
Communication Research Institute of St. Thomas	LINC
<u>GEORGIA</u>	
Emory University	IBM 1620
<u>ILLINOIS</u>	
Chicago, University of	IBM 7090* - IBM 1401
Northwestern University	LINC - IBM 1710+
<u>INDIANA</u>	
Indiana University	IBM 1410
<u>KANSAS</u>	
Kansas, University of	IBM 7040*
<u>LOUISIANA</u>	
Tulane University	IBM 1410 - IBM 1401
<u>MARYLAND</u>	
Johns Hopkins University	IBM 1401 - LINC (2)
Maryland, University of, Medical School	IBM 1620
<u>MASSACHUSETTS</u>	
Massachusetts General Hospital	PDP 4+
Harvard University	IBM 1710 - PDP 4 - IBM 1620+
Massachusetts Institute of Technology	LINC (3)
Clark University	IBM 1620
<u>MINNESOTA</u>	
Mayo Association	IBM 1620

<u>MISSOURI</u>			
Missouri, University of		IBM 1410+	
Psychiatric Research Foundation of Missouri		IBM 1710+	
Central Institute for the Deaf		LINC	
Washington University		LINC	
<u>NEW JERSEY</u>			
Seton Hall University		IBM 1620	
<u>NEW MEXICO</u>			
New Mexico Highland University		IBM 1620	
<u>NEW YORK</u>			
New York, State University of, Downstate Medical Center		IBM 1620+	
New York, University of, Buffalo		IBM 7044* - IBM 1620	
Health Research, Inc. - Roswell Park Div.		IBM 1620	
Memorial Hospital for Cancer and Allied Diseases		CDC 160A	
New York University Medical Center		CDC 1604* - CDC 160A	
Yeshiva University		CDC 160A	
New York, State University of, Upstate Medical Center		IBM 1620+	
<u>NORTH CAROLINA</u>			
North Carolina, University of		IBM 1410* - LINC - IBM 1620	
Duke University		LINC - IBM 7072*	
Bowman Gray School of Medicine, Wake Forest College		LINC - IBM 1620*	
<u>OHIO</u>			
Cincinnati, University of, College of Medicine		IBM 7040	
Western Reserve University		GE 225+ - IBM 1620	
Fels Research Institute		IBM 1620	
<u>OKLAHOMA</u>			
Oklahoma, University of		IBM 1620 - IBM 1431	
<u>OREGON</u>			
Medical Research Foundation of Oregon Inc. (Oregon Regional Primate Research Center)		SDS-920+	
Oregon, University of, Medical School		IBM 1410	
<u>PENNSYLVANIA</u>			
Pennsylvania, University of		CDC 160A	
Presbyterian Hospital in Philadelphia		LINC	
<u>RHODE ISLAND</u>			
Brown University		LINC	
<u>TENNESSEE</u>			
Tennessee, University of		IBM 1620	
<u>TEXAS</u>			
Texas, University of, Galveston		IBM 1410* - IBM 1620	
Texas, University of, Houston		IBM 1710	
Baylor University		IBM 1410+	
<u>UTAH</u>			
Utah, University of	CDC 3200	<u>WASHINGTON</u>	
		Washington, University of	PB 440 - LINC
<u>VIRGINIA</u>			
Medical College of Virginia	RPC 4000	<u>WISCONSIN</u>	
		Wisconsin, University of	LINC

The Background of INTERNIST-I and QMR

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During my tenure as Chairman of the Department of Medicine at the University of Pittsburgh, 1955 to 1970, two points became clear in regard to diagnosis in internal medicine. The first was that the knowledge base in that field had become vastly too large for any single person to encompass it. The second point was that the busy practitioner, even though he knew the items of information pertinent to his patients correct diagnosis, often did not consider the right answer particularly if the diagnosis was an unusual disease.

I resigned the position of Chairman in 1970 intending to resume my position as Professor of Medicine. However, the University saw fit to offer me the appointment as University Professor (Medicine). The University of Pittsburgh follows the practice of Harvard University, established by President James Bryant Conant in the late 1930s, in which a University Professor is a professor at large and reports only to the president of the university. He has no department, no school and is not under administrative supervision by a dean or vice-president. Thus the position allows maximal academic freedom.

In this new position I felt strongly that I should conduct worthwhile research. It was almost fifteen years since I had worked in my chosen field of clinical investigation, namely splanchnic blood flow and metabolism, and I felt that research in that area had passed me by. Remembering the two points mentioned earlier -- the excessive knowledge base of internal medicine and the problem of considering the correct diagnosis -- I asked myself what could be done to correct these problems. It seemed that the computer with its huge memory could correct the first and I wondered if it could not help as well with the second.

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At that point I knew no more about computers than the average layman so I sought advice. Dr. Gerhard Werner, our Chairman of Pharmacology, was working with computers in an attempt to map all of the neurological centers of the human brain stem with particular reference to their interconnections and functions. He was particularly concerned about the actions of pharmacological agents on this complex system. Working with him on this problem was Dr. Harry Pople, a computer scientist with special interest in "artificial intelligence". The problem chosen was so complex and difficult that Werner and Pople were making little progress.

Gerhard listened patiently to my ideas and promptly stated that he thought the projects were feasible utilizing the computer. In regard to the diagnostic component of my ambition he strongly advised that "artificial intelligence" be used. Pople was brought into the discussion and was greatly interested, I believe because of the feasibility of the project and the recognition of its practical application to the practice of medicine.

The upshot was that Pople joined me in my project and Werner and Pople abandoned the work on the brain stem. Pople knew nothing about medicine and I knew nothing about computer science. Thus the first step in our collaboration was my analysis for Pople of the diagnostic process. I chose a goodly number of actual cases from clinical pathological conferences (CPCs) because they contained ample clinical data and because the correct diagnoses were known. At each small step of the way through the diagnostic process I was required to explain what the clinical information meant in context and my reasons for considering certain diagnoses. This provided to Pople insight into the diagnostic process. After analyzing dozens of such cases I felt as though I had undergone a sort of "psychoanalysis".

From this experience Pople wrote the first computer diagnostic programs seeking to emulate my diagnostic process. This has led certain "wags" to nickname our project "Jack in the box". For this initial attempt Pople used the LISP computer language. We were granted access to the PROPHET PDP-10, a time-sharing mainframe maintained in Boston by the National Institutes of Health (NIH) but devoted particularly to pharmaco-

logical research. Thus we were interlopers.

The first name we applied to our project was DIALOG, for diagnostic logic, but this had to be dropped because the name was in conflict with a computer program already on the market and copyrighted. The next name chosen was INTERNIST for obvious reason. However, the American Society for Internal Medicine publishes a journal entitled "The Internist" and they objected to our use of INTERNIST although there seems to be little relationship or conflict between a printed journal and a computer software program. Rather than fight the issue we simply added the Roman numeral one to our title which then became INTERNIST-I, which continues to this day.

Pople's initial effort was unsuccessful, however. He diligently had incorporated details regarding anatomy and much basic pathophysiology, I believe because in my initial CPC analyses I had brought into consideration such items of information so that Pople could understand how I got from A to B etc. The diagnostician in internal medicine knows, of course, much anatomy and pathophysiology but these are brought into consideration in only a minority of diagnostic problems. He knows, for example, that the liver is in the right upper quadrant and just beneath the right leaf of the diaphragm. In most diagnostic instances this information is "subconscious".

Our first computer diagnostic program included too many such details and as a result was very slow and frequently got into analytical "loops" from which it could not extricate itself. We decided that we had to simplify the program but by that juncture much of 1971 had passed on.

The new program was INTERNIST-I and even today most of the basic structure devised in 1972 remains intact. INTERNIST-I is written in INTERLISP and has operated on the PDP-10 and the DEC 2060. It has also been adapted to the VAX 780. Certain younger people have contributed significantly to the program, particularly Dr. Zachary Moraitis and Dr. Randolph Miller. The latter interrupted his regular medical school education to spend the year 1974-75 as a fellow in our laboratory and since finishing his formal medical education in 1979 has been active as a full time faculty member of the team. Several Ph.D. candidates in computer science have also made significant contributions as have dozens of medical students during electives on the project.

INTERNIST-I is really quite a simple system as far as its operating system or inference engine is concerned. Three basic numbers are concerned in and manipulated in the ranking of elicited disease hypotheses. The first of these is the importance (IMPORT) of each of the more than 4,100 manifestations of disease which are contained in the knowledge base. IMPORTS are a global representation of the clinical importance of a given finding graded from 1 to 5, the latter being maximal, focusing on how necessary it is to explain the manifestation regardless of the final diagnosis. Thus massive splenomegaly has an

IMPORT of 5 whereas anorexia has an IMPORT of 1. Mathematical weights are assigned to IMPORT numbers on a non-linear scale.

The second basic number is the evoking strength (EVOKS), the numbers ranging from 0 to 5. The number answers the question, that given a particular manifestation of disease, how strongly does one consider disease A versus all other diagnostic possibilities in a clinical situation. A zero indicates that a particular clinical manifestation is non-specific, i.e. so widely spread among diseases that the above question cannot be answered usefully. Again, anorexia is a good example of a non-specific manifestation. The EVOKS number 5, on the other hand, indicates that a manifestation is essentially pathognomonic for a particular disease.

The third basic number is the frequency (FREQ) which answers the question that given a particular disease what is the frequency or incidence of occurrence of a particular clinical finding. FREQ numbers range from 1 to 5, one indicating that the finding is rare or unusual in the disease and 5 indicating that the finding is present in essentially all instances of the disease.

Each diagnosis which is evoked is ranked mathematically on the basis of support for it, both positive and negative. Like the import number, the values for EVOKS and FREQ numbers increase in a non-linear fashion. The establishment or conclusion of a diagnosis is not based on any absolute score, as in Bayesian systems, but on how much better is the support of diagnosis A as compared to its nearest competitor. This difference is anchored to the value of an EVOKS of 5, a pathognomonic finding.

When the list of evoked diagnoses is ranked mathematically on the basis of EVOKS, FREQ and IMPORT, the list is partitioned based upon the similarity of support for individual diagnoses. Thus a heart disease is compared with other heart diseases and not brain diseases since the patient may have a heart disorder and a brain disease concomitantly. Thus apples are compared with apples and not oranges.

When a diagnosis is concluded, the computer consults a list of interrelationships among diseases (LINKS) and bonuses are awarded, again in a non-linear fashion for numbers ranging from 1 to 5 -- 1 indicating a weak interrelationship and 5 a universal interrelationship. Thus multiple interrelated diagnoses are preferred over independent ones provided the support for the second and other diagnoses is adequate. Good clinicians use this same rule of thumb. LINKS are of various types: PCED is used when disease A precedes disease B, e.g. acute rheumatic fever precedes early rheumatic valvular disease; PDIS - disease A predisposes to disease B, e.g. AIDS predisposes to pneumocystis pneumonia; CAUS - disease A causes disease B, e.g. thrombophlebitis of the lower extremities may cause pulmonary embolism; and COIN - there is a statistical interrelationship between disease A and disease B but scientific medical information is not explicit on the

relationship, e.g. Hashimoto's thyroiditis coincides with pernicious anemia, both so called autoimmune diseases.

The maximal number of correct diagnoses made in a single case analysis is, to my recollection, eleven.

In working with INTERNIST-I during the remainder of the 1970s several important points about the system were learned or appreciated.

The first and foremost of these is the importance of a complete and accurate knowledge base. Omissions from a disease profile can be particularly troublesome. If a manifestation of disease is not listed on a disease profile the computer can only conclude that that manifestation does not occur in the disease, and if a patient demonstrates the particular manifestation it counts against the diagnosis. Fortunately, repeated exercise of the diagnostic system brings to attention many inadvertent omissions. It is important to establish the EVOKS and FREQ numbers as accurately as possible. Continual updating of the knowledge base, including newly described diseases and new information about diseases previously profiled, is critical. Dr. Edward Feigenbaum recognized the importance of the accuracy and completeness of knowledge bases as the prime requisite of expert systems of any sort. He emphasized this point in his keynote address to MEDINFO-86 (1).

Standardized, clear and explicit nomenclature is required in expressing disease names and particularly in naming the thousands of individual manifestations of disease. Such rigidity can make the use of INTERNIST-I difficult for the uninitiated user. Therefore, in QMR more latitude and guidance is provided the user. For example, the user of INTERNIST-I must enter ABDOMEN PAIN RIGHT UPPER QUADRANT exactly whereas in QMR the user may enter PAI ABD RUQ and the system recognizes the term as above.

The importance of "properties" attached to the great majority of clinical manifestations was solidly evident. Properties express such conditions that if A is true then B is automatically false (or true as the case may be). The properties also allow credit to be awarded for or against B as the case may be. Properties also provide order to the asking of questions in the interrogative mode. They also state prerequisites and unrequisites for various procedures. As examples, one generally does not perform a superficial lymph node biopsy unless lymph nodes are enlarged (prerequisite). Similarly, a percutaneous liver biopsy is inadvisable if the blood platelets are less than 50,000 (unrequisite).

It became clear quite early in the utilization of INTERNIST-I that systemic or multisystem diseases had an advantage versus localized disorders in diagnosis. This is because systemic diseases have very long and more inclusive manifestation lists. It became necessary, therefore, to subdivide systemic diseases into various components when appropriate. Systemic lupus erythematosus provides a good example. Lupus

nephritis must be compared in our system with other renal diseases and such comparison is allowed by our partitioning algorithm. Likewise, cerebral lupus must be differentiated from other central nervous system disorders. Furthermore, either renal lupus or cerebral lupus can occur at times without significant clinical evidence of other systemic involvement. In order to reassemble the components of a systemic disease we devised the systemic LINK (SYST) which expresses the interrelationship of each subcomponent to the parent systemic disease.

It became apparent quite early that expert systems like INTERNIST do not deal with the time axis of a disease well at all, and this seems to be generally true of expert systems in "artificial intelligence". Certain parameters dealing with time can be expressed by devising particular manifestations, e.g. a blood transfusion preceding the development of acute hepatitis B by 2 to 6 months. But time remains a problem which is yet to be solved satisfactorily including QMR.

It has been clearly apparent over the years that both the knowledge base and the diagnostic consultant programs of both INTERNIST-I and QMR have considerable educational value. The disease profiles, the list of diseases in which a given clinical manifestation occurs (ordered by EVOKS and FREQ), and the interconnections among diseases (LINKS) provide a quick and ready means of acquiring at least orienting clinical information. Such has proved useful not only to medical students and residents but to clinical practitioners as well. In the interrogative mode of the diagnostic systems the student will frequently ask "Why was that question asked?" An instructor can either provide insight or ready consultation of the knowledge base by the student will provide a simple semi-quantitative reason for the question.

Lastly, let the author state that working with INTERNIST-I and QMR over the years seems to have had real influence on his own diagnostic approaches and habits. Thus my original psychoanalysis when working with Pople has been reinforced.

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Artificial Intelligence in Medicine: A Personal Retrospective on its Emergence and Early Evolution

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ABSTRACT

Methods of artificial intelligence were gradually introduced into clinical decision-making research from 1970 to 1974. Evolving from pattern recognition and general A.I. problem-solving ideas, such methods helped researchers crystallize the notions of knowledge-based systems by the mid-1970s. In 1978 the early systems gave way to either second-generation frameworks for general consultative reasoning or to new, more sophisticated knowledge representations. This paper traces some of the major events in the early evolution of AIM systems, with emphasis on the developments at the Rutgers Resource, in which the author participated.

Prelude: The State-of-the-Art in Computer Assisted Clinical Decision-Making in 1970

The first proposals to apply artificial intelligence (A.I.) to clinical decision-making evolved at Rutgers University in 1970 during the preparation of a grant proposal to the NIH Biotechnology Resources Program. They followed a decade of rapid advances in statistical methods for computer-aided diagnosis, initiated by the pioneering efforts of Lipkin, Hardy, and Engle at the New York Cornell Medical School [L-4], who first explored logical and probabilistic approaches to the diagnosis of hematological disorders. The applicability of Bayesian inference, utility theory, and Boolean logic

to diagnostic problems was made widely known within the biomedical research community through Ledley and Lusted's article in *Science* [L-1] in 1959. Warner subsequently popularized the use of Bayes' rule to calculate posterior probabilities of diseases [W-1], while discriminant analysis methods were applied to thyroid disease diagnosis [O-1] and to multi-disease screening through the Cornell Index. Classical hypothesis-testing methods for disease classification were used by Collen and his colleagues at Kaiser Permanente based on the wealth of data collected in their multi-phasic screening center. Signal analysis and pattern recognition methods were applied in ECG interpretation, while a decision-tree approach characterized Howard Bleich's well-known program on acid-base balance disorders [B-1]. This meant that by 1970 all traditional formalizations of reasoning had been applied to computer-assisted decision-making problems. Yet, despite this progress there appeared to be little enthusiasm in the medical community at large for computer-based methods.

Some of the difficulties in acceptability could then, as now, be blamed on the awareness of the complexities of human diagnostic reasoning that were not captured by methods of formal logic or probabilistic inference. Many of these problems were discussed as early as 1963 during a conference held at the University of Michigan on "The Diagnostic Process." For the proceedings, edited by Jacquez [J-1] it is striking to see a clear identification of topics that still preoccupy researchers: multi-disease discrimination, temporal courses of diseases, causal relationships between disease entities, and the contrast between describing an individual patient's problems vs. the statistical characterization of diseases. In 1965, Ledley published a book on the *Uses of Computers in Biology and Medicine* [L-2]. It not only summarized some of his early work in the field of logical diagnosis, but also gave many practical examples of the application of clustering methods and utility theory in

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medical diagnosis. It is again interesting to see that Ledley anticipated many of the concerns that have now become routine in the application of decision analysis and other formal methods in clinical decision-making (as evidenced by the many articles in the *Journal of Medical Decision-Making*). In 1968 Lusted summarized his experiences with Bayesian and likelihood methods for diagnosis in the book, *Introduction to Medical Decision-Making* [L-5], which became for many years the only widely available monograph on the subject.

It was in this same year that I first became involved with clinical decision-making problems. My doctoral advisor at the University of Hawaii, Professor Michael S. Watanabe, suggested that I contact Dr. Robert Nordyke of the Straub Clinic to investigate the possible application of pattern recognition methods in medical diagnosis. Nordyke had accumulated a large data base of thyroid disease records, and wished to have them analyzed. He also wanted to see if it would be practical to develop a computer program to help him screen the large number of non-thyroid conditions that were referred to his specialty clinic. Over the previous five years, Watanabe had developed several pattern recognition approaches that selected only the most discriminating combinations of features for a decision. He suggested that I investigate the application of the CLAFIC (class-featuring information compression) method in particular to the medical diagnostic problem. In working with Nordyke, I rapidly found that one of the major problems in developing a computer based screening and consultation system did indeed consist of selecting the most discriminating sets of manifestations. Over the next couple of years, I developed a group of programs for carrying out sequential diagnosis based on sets of symptoms, signs, and laboratory tests for thyroid disease [K-1], [N-1]. These were placed into operation at Straub within Nordyke's thyroid clinic helping automate the production of reports and provide a statistical analysis of the thyroid data. However, even while completing this work in 1970 it became clear that there would be problems of acceptability with the system. In observing the reaction of other physicians to the use of Nordyke's programs, it was clear that while trusting his data and his interpretations, they were very suspicious of the probabilities and discrimination scores produced by my programs based on the same data. It was somewhat disheartening to see that the work I had just completed was unlikely to be widely used unless the "black box" nature of the mathematical processing was somehow explained.

It was at this juncture, during job interviews, that I met Professor Saul Amarel, who was proposing to build

a research group at Rutgers University devoted to the application of advanced computer science methods (particularly artificial intelligence) to problems of biomedical research and medical practice. Having become acquainted with some of the artificial intelligence programs for game playing and planning of the time, I was skeptical that they could help in dealing with practical and "noisy" problem solving such as occurs in clinical diagnosis. In speaking with Amarel he brought to my attention the possibilities of more general representational frameworks, which could be used in characterizing real, complex interpretation problems. In particular, he pointed to the DENDRAL project at Stanford as a case where detailed knowledge of plausible chemical structures could be used to guide the search for an interpretation of a mass spectrogram, rather than applying pattern recognition methods directly. It was in

the following year that I began to think about the notion of finding a more detailed description of disease processes that could help provide a structure for diagnostic reasoning that went beyond a purely phenomenological association of symptoms with diseases. Only in that way, by "reasoning like a physician," would our computer based methods become acceptable to physicians. I did not realize at the time that this represented a decisive change in my thinking, moving from a purely engineering approach towards a deeper consideration of the "cognitive model" that the human diagnostician uses.

As the result of the meetings with Amarel I came to Rutgers and joined with him and other faculty from the newly-formed Department of Computer Science, as well as faculty from the biological sciences, psychology, ecology, and the medical school, in writing a proposal to the National Institutes of Health to establish a *Research Resource on Computers in Biomedicine* at Rutgers. This was done with the encouragement of Dr. William Raub, who headed the biotechnology resources program of the NIH at that time. Raub had been a student of Dr. William Yamamoto, at the University of Pennsylvania, and was very interested in the application of a wider set of biomathematical modeling and simulations techniques in biomedical research and practice. It was also at about this time that Dr. William Schwartz at Tufts New England Medical Center, working in collaboration with Dr. G. A. Gorry at M.I.T., published an influential article entitled "Medicine and the Computer: The Promise and Problems of Change" in the *New England Journal of Medicine*, in which he eloquently proposed that the more routine tasks of the physician would be good candidates for computerization [S-1]. Gorry had been a

pioneer in developing sequential statistical methods for test selection in diagnosis [G-1], and was at this time also confronting the problems of computerized clinical decision-making by studying the cognitive processes of human diagnosticians [G-2]. As chance would have it, I had interviewed with Schwartz in 1970, in the course of which he described to me his hope of establishing a department of medical computer science within the medical school. As things turned out it was the Tufts-M.I.T. collaborations that he encouraged and participated in that became important catalysts in the development of AIM ideas [S-2].

The NIH approved our Rutgers Resource in 1971, making it the first focus of research in the application of artificial intelligence to problems of biomedical inquiry. Saul Amarel was the Principal Investigator, and I was placed in charge of the clinical decision-making area. As I have described above, the time was ripe for the development of alternative schemes for cognitive representation and inferencing in dealing with diagnostic problems.



Saul Amarel, first P.I. of the Rutgers Resource trying out a program on the PDP-10 computer.

During the next four years these seeds planted at Rutgers, at Stanford, Tufts-M.I.T., and the University of Pittsburgh all germinated and produced the first generation of knowledge-based artificial intelligence systems for clinical decision-making.

Early Developments of Artificial Intelligence in Medicine: 1970-74

When I joined Rutgers in 1970 my first research priority was to extend the pattern recognition methods that I had developed to a broader class of problems, continuing the research with Professor Watanabe. However, as soon as the Rutgers Research Resource on Computers in Biomedicine was funded, I started working on ways of formulating alternative formalizations of the diagnostic process. At first, one alternative that presented itself was to try syntactic methods of pattern recognition which might enable one to describe a disease in terms of grammatical rules. During the fall of 1971, I was joined by Dr. Lyon Hyams of Rutgers Medical School, and together we tried to develop grammatical rules for thyroid disease, hematologic disorders and other problems that we were acquainted with. Hyams was an M.D. bio-statistician who felt very strongly that physicians would need to learn how to think in Bayesian terms while we also endeavored to make computers "think" more like human specialists. We explored the application of Bayesian methods in medical education and did very well in this. However, Hyams' untimely death in 1971 brought an end to these investigations.

In the last months of working together he had introduced me to Dr. Aran Safir, an ophthalmologist at the Mt. Sinai School of Medicine who became very interested in the possibility of using computer models to represent those aspects of medical reasoning which involve encyclopedic retrieval of knowledge, thereby leaving the physician free to pursue the more fruitful nuances of the problem solving process itself. In the fall of 1971, we were joined by Sholom Weiss as a research assistant pursuing his doctoral studies. Together we experimented with grammatical representations for ophthalmological diseases but rapidly found them wanting. It was at this point that a key conceptual breakthrough took place. In our discussions with Safir it became clear that to "speak the language of the clinician," one needed to represent the cause and effect relationships that explain the pathogenesis of a disease. This led us to examine the nature of causes and effects. At first we considered developing a model of the normal physiology that could be subject to perturbations describing pathological conditions. Due to the myriad patterns of normal values of physiological parameters we soon abandoned this approach. We then struck on the crucial idea that one ought to look at *qualitative descriptions of pathophysiological states*, such as "elevated intraocular pressure," rather than specific numerical values of physiological parameters. The

notion of a pathophysiological state as an abstract summary of observable events followed shortly afterwards. Sholom Weiss helped formulate a working computer model of these ideas, and produced a causal network (CASNET) model for glaucoma. Safir had suggested that we concentrate on this disease because of its significance as a major cause of blindness. In addition, because it had fairly well-understood mechanisms that influenced the selection of therapy, the chances of succeeding in the causal modeling were good. Yet at the same time, the disease could be resistant to treatment, making consultation with a specialist important. The possibility of capturing the knowledge and expertise of the specialist in a computer program would help make it more widely available.

A first version of CASNET was run retrospectively on glaucoma data from the Mt. Sinai School of Medicine in the Fall of 1972. We gave the first scientific presentation of this work at the December 1972 IEEE Conference on Decision and Control in a session chaired by Professor K. S. Fu entitled "Modern Pattern Recognition" [K-2]. Our paper stressed how one could apply different strategies of data acquisition using the same causal network as the underlying model of knowledge. During early 1973 we continued to develop the glaucoma model and realized that it could be viewed as a three layered representation of knowledge. At the lowest level we placed the actual data or manifestations of the patient, at the second level the pathophysiological states summarizing the data, and at a third level the diagnostic hypotheses that describe more broadly the mechanisms of disease. For instance, tension readings on the eye within a certain high range at the first level can map into the concept of abnormally elevated intraocular pressure which is inferred as a pathophysiological state. Likewise, a measurement of very small angle grades in the anterior segment of the eye by gonioscopy can be mapped into an abstracted pathophysiological state of "angle closure," and certain patterns of visual field loss measured on the tangent screen are described by human experts as representing a "nasal step," or an "enlargement of the blind spot," both patterns of field loss associated with glaucoma. It was Safir's suggestion that states such as these be linked causally to describe the mechanisms of glaucoma. Sholom Weiss and I proposed that while one linked pathway of states could be used to define one variant of glaucoma (such as angle closure glaucoma), another pathway could define open angle glaucoma, and yet another, a secondary glaucoma due to a mass in the anterior segment of the eye, and so on. We also suggested that in order to take into account statistical

variability among patients that the mapping between observations and pathophysiological states would have to involve some probability-like measures of uncertainty, whereas the mapping from pathways of states to diseases might be purely definitional and deterministic.

Furthermore, because of the inherent variability of biological processes the causal links themselves would have to be weighted: there could be no Aristotelian fixed and unique relations between states. What emerged was a probabilistic network of causes and effects.

As we put more and more glaucoma knowledge into this representation it also became clear that a diagnostic program alone would be much less exciting to physicians than a program that gave advice on the latest treatments, particularly if they referred to controversial topics. Safir deliberately selected a number of situations where surgical vs. medical treatment was a matter of argument, and we were able to extend the representation to a fourth level, which contained the treatments or actions that would be triggered from a diagnosis. It was at this time that I suggested that we consider Feinstein's idea that there must be an "environmental" component to treatment which customizes a standard therapeutic regime to the peculiarities of a patient and his environment [F-2]. This meant that rather than having a fixed set of treatments keyed off diagnostic outcomes, the nuances of therapy are adjusted to take into account the specific set of patient manifestations that make an individual patient's situation unique. For instance, someone who has a history of being resistant to a certain kind of medication may be chosen for a nonstandard alternative, or someone who has a history of poor compliance may be recommended for more frequent checkups and treatment that relies less on his own administration of the medications.

Our progress with the glaucoma consultation program was sufficiently rapid that Safir suggested taking a prototype to demonstrate at the annual meeting of the Association for Research and Ophthalmology. It was at this meeting in April 1973 that we were able to enlist the help of several distinguished clinical researchers in glaucoma, including Dr. Bernard Becker, co-author of the major textbook on the diagnosis and treatment of the glaucomas. He was initially joined by his colleague, Dr. Steven Podos of Washington University, and by Dr. Irvin Pollack of Johns Hopkins University. It was very reassuring for us to see that specialists in glaucoma felt that our causal models of disease did indeed correspond to many of their own paths of reasoning. At the same

time, they made us aware of the limitations of the first prototype and suggested many improvements.

It was around this time that I first met Ted Shortliffe, who was working on his doctoral dissertation at Stanford University. Shortliffe was already committed to the development of a consultant program in infectious diseases, and when he visited the Rutgers Resource we discussed the problems of reasoning under uncertainty and the need to develop consultation systems that would be understandable to the clinician. At that point Shortliffe was experimenting with reasoning strategies motivated by theorem proving techniques. He felt that PLANNER-type consequent theorems provided a good mechanism for goal directed problem solving, and his initial control structure for MYCIN was designed to "avoid the shotgun approach of a diagnostic system based solely on mechanisms analogous to antecedent theorems." Shortliffe was also strongly influenced towards a modular representation in the form of rules by Waterman's use of production systems in the form of situation-action rules, and by the heuristic DENDRAL project experience at Stanford. There is no question but that even during these early stages of research in 1973 there was a strong contrast between the emphasis of Shortliffe's work on the modular and judgmental components of clinical decision-making as opposed to the causal "architectural approach" taken by our group at Rutgers. Meanwhile, we also became aware of work being carried out by Harry Pople on problems of abduction in biomedical theory formation. After initiating a collaboration with Dr. Jack Meyers on consultation in internal medicine, he applied many of the ideas of abductive reasoning to diagnosis. In fact, the first version of their consultation program was called DIALOG (for diagnostic logic) [P-2], and stressed the hierarchical nature of the organization of medical knowledge. Qualitative levels of uncertainty were used to link manifestations to the disease entities. While the research emphasis of the Pittsburgh group may have seemed quite different from ours and from that of the Stanford and Tufts-M.I.T. groups [P-1], in retrospect we all shared the same concerns of introducing heuristic uncertainty measures, modularizing knowledge, and providing more flexible strategies of consultation that would be acceptable to human experts.

Steps Towards Consolidation of AIM: 1974-78

The year 1974 saw the completion of the first two theses in artificial intelligence in medicine. Sholom Weiss completed his work at Rutgers on the causal model approach to medical decision-making [W-2], while

Ted Shortliffe at Stanford completed his rule based approach for therapy advice in infectious diseases [S-4].

It was also in 1974 that a second research resource sponsored by the NIH's Division of Research Resources was established at Stanford. SUMEX-AIM made explicit in its title what was only implicit in the Rutgers Resource--the advancement of artificial intelligence in medicine [F-3]. This resource also provided time-shared computing facilities (initially on a PDP-10, later on a DEC-20) which helped many of the fledgling research groups get started with more sophisticated programs. At the same time, with the strong support of Dr. William Baker at the Biotechnology Research Resources Program of NIH, SUMEX fostered the idea of shared intellectual and physical computing resources through the development of an AIM community. At Stanford, Shortliffe's research continued to be the major focus of investigations into clinical decision-making. Together with his advisor, Bruce Buchanan, he developed a model of inexact reasoning based on non-probabilistic confidence factors [S-5]. This served as an important component of the inference mechanism of MYCIN [S-6].

The work on artificial intelligence in medicine became more widely known when a regular series of AIM workshops sponsored by the Rutgers Resource were begun in 1975. The first workshop was small and brought together the AIM researchers themselves. It was most valuable in informally exchanging tips on interdisciplinary collaboration problems, and in clarifying some of the assumptions behind each group's research approach. The workshop in 1976 was larger, and included presentations by many researchers taking alternative approaches to medical decision-making and modeling. These meetings helped disseminate artificial intelligence ideas and set the stage for the introduction of knowledge-based methods in a number of other research areas (geology, chemistry, and engineering).

Within the Rutgers Resource during 1974-76 we were able to broaden the scope of our collaborations in ophthalmology. Thanks to Safir's efforts, an ophthalmological network of glaucoma specialists (ONET) was formed to systematically enter their knowledge and expertise in glaucoma diagnosis and therapy into our program. Sholom Weiss joined the Mt. Sinai School of Medicine as a researcher who became one of the first "knowledge engineers," before the term had been coined. He traveled tirelessly around the country working with our collaborators at various medical centers: Washington University, Johns Hopkins University, University of Miami, and the University of Illinois, as well as Mt. Sinai. By 1976, the glaucoma

consultation program had been expanded to handle a large variety of secondary glaucoma conditions, as well as being much more sophisticated in the primary glaucomas. It was at this point that we proposed to test the system by having it challenged publicly at the meeting of the American Academy of Ophthalmology that was held in Las Vegas in October, 1976. A Symposium on Glaucoma, sponsored for the National Society for the Prevention of Blindness, included five specialists and a moderator (Dr. Anderson), with our computer program as the sixth "panelist." We also demonstrated our program at the Academy's scientific exhibit, and gathered cases from experts who wished to challenge the system. During the Symposium on Glaucoma, the computer was able to respond to all the cases presented to it. It provided a summary of the diagnostic and treatment recommendations which could then be compared to the comments of the specialists. The resulting exchanges of the panelists and the commentary on the computer output were transcribed in the book, *Discussions on Glaucoma*, edited by Drs. Lichter and Anderson [L-3]. The program did very well in matching the diagnostic conclusions of the specialists. There were some discrepancies in the treatment recommendations, but these involved no more variation than that found among the specialists themselves. Our most anxious moment took place just before the panel was about to start its discussions. Someone tripped over and unplugged the phone line that connected our display terminal in the immense labyrinth of the Las Vegas Hilton Hotel conference rooms. It reminded us most vividly of the fragility of the technology. Luckily, the connection was re-established one minute before start time. With the success of this demonstration, the consultation system proved that the expertise of specialists from around the country could be pooled and then through computer networking disseminated to a large number of non-specialists. The CASNET system was the first example of a high performance prototype covering detailed diagnosis and treatment knowledge in a specialty which could actually give advice at the level of an expert consultant [W-3], [W-4]. Kevin Kern helped program the full-fledged CASNET system, while Peter Politakis joined in subsequent knowledge-base refinement research.

Also during 1976 Shortliffe published his thesis on MYCIN [S-6], and the group at Stanford continued the development of the MYCIN program, leading subsequently to an evaluation of the system by a group of specialists in infectious diseases [Y-1]. These results showed that a rule based system could be brought to a high level of performance. The work at Stanford was



Peter Politakis (seated) presenting his research system on knowledge-base refinement to S. Weiss, K. Kern, and C. Kulikowski (standing l. to r.)

widely disseminated by Drs. Feigenbaum and Lederberg, who were able to convince many skeptical biomedical scientists and computer scientists of the importance of domain knowledge as the basis of practical problem solving systems. It was Edward Feigenbaum who popularized the phrase "knowledge-based systems" [F-1]. An early example of such a system in clinical decision-making, besides CASNET, DIALOG, and MYCIN, was the Digitalis Advisory System developed by the Tufts-M.I.T. group [G-3]. It showed that a mathematical compartmental model of digitalis release could be used in conjunction with qualitative reasoning to capture clinical expertise in the administration of digitalis. An important article by Pauker, Gorry, Kassirer, and Schwartz in the *American Journal of Medicine* in 1976 [P-1], gave a first outline of how Minsky's frame-based structures [M-1] for describing and recalling information about a present illness could be used in a consultation program. The article gave a number of examples of how general symptoms could trigger a set of related diagnostic entities into short term memory where they would be subject to hypothesis testing. The Present Illness Program (PIP) was critical in showing that the process of gathering medical information, generating hypotheses, testing them, and selecting new information together represented a complex cycle of inferencing that did not easily fit into a traditional formal framework. At this time, the work on INTERNIST was being extended by Pople to involve reasoning about multiple diseases and associations of a causal nature [P-3]. The CADEUCEUS program that is still evolving shows the degree to which complex representations of knowledge

are needed for these tasks. These practical experiences with programming experiments were supported by psychological research into problems of clinical judgment and practice carried out by Elstein and his colleagues [E-1], [E-2].

Conclusion: 1978 as the End of the First AIM Cycle

In looking back on the early evolution of artificial intelligence methods in clinical decision-making, it is easy to mark 1978 as the end of the first cycle of development. It was in that year that an excellent review of the first generation systems was published by Szolovits and Pauker [S-7], who stressed the need for both categorical and probabilistic reasoning as well as complex knowledge structures for diagnostic reasoning. Also at this time, Schoolman and Bernstein gave broad dissemination to some of the early AIM work in an article in *Science* [S-1]. The previous year, 1977, had seen the first Symposium on Computer Applications in Medical Care (SCAMC) highlight the AIM systems in its session of clinical decision-making. The following year marked the emergence of general model-building "shells" based on AIM work: EMYCIN [V-5] at Stanford and EXPERT [W-5] at Rutgers. These served as vehicles for developing consultation expert systems in many different medical and non-medical domains, thereby demonstrating the generality of the knowledge-based approach. The first generation, which was bound to experimentation with decision prototypes for specific diseases, had come to an end.

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