6.
History of Funding for NMR Research

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INTRODUCTION

Government policies related to funding of medical device research and development by universities and manufacturers can have important impacts on the evolution of technology and the shape of particular device industries. The purpose of this chapter is to review the history of government funding for NMR research in the United States and in England and Scotland where much of the early work on NMR imaging was performed. Policy issues that emerge from this review are discussed in the final section of this chapter.[1]

[1]Readers who are not interested in the details of government funding of NMR research may want to read only the final section of this chapter,

UNITED STATES

National Institutes of Health

Over the past decade, the National Institutes of Health (NIH) have supported research relating to NMR imaging, biomedical applications of NMR relaxation-time parameters, and biomedical applications of NMR spectroscopy. Although NIH has provided some funds for the development and use of software and ancillary hardware, NIH has not provided, and does not plan to provide, support to clinical or research institutions to be used either to develop or purchase NMR imaging machines for use in human imaging.

Intramural Research

Conventional Spectroscopy.—NIH has had an active intramural program of research involving conventional chemical and physical applications of NMR spectroscopy for many years. A description of these activities is beyond the scope of this report.

Instrumentation and Imaging Techniques. -Dr. David Hoult, a physicist and electronics engineer formerly involved with in vivo phosphorus spectroscopic research at Oxford University, has been at the Biomedical Engineering and Instrumentation Branch of NIH since **1977.** Over the past **6** years, his research at NIH has focused on NMR imaging instrumentation and techniques. In addition to developing the rotating frame technique of NMR imaging (94) and systematically exploring the parameters affecting image quality, resolution, contrast and signal-to-noise ratio, Hoult has built a small-bore (30 cm diameter) 0.117 tesla (T) NMR imager. The imager as yet has been used only to image phantoms, but may be used for studies of animals or newborns in the future.

Physiology.--Dr. Robert Balaban, Senior Staff Fellow at the National Heart, Lung, and Blood Institute, has been studying physiological applications of phosphorus, sodium, and nitrogen NMR spectroscopy for the past 3½ years. In his research at NIH Balaban has employed in vivo ^{31}P NMR spectroscopy to measure the phosphorus content of cardiac muscle under varying physiological conditions, has measured the kinetics of metabolic reactions such as the transfer of phosphorus from adenosine triphosphate to creatine phosphate, and has studied sodium transport across plasma membranes and the concentration of various nitrogen-containing buffers in various tissues in the body.

Clinical Research.—Using funds contributed from many of its Institutes, NIH has purchased a 0.5 T whole-body NMR imaging system from Picker International. This system has been delivered to NIH and clinical studies were scheduled to begin in September 1983. This system, which was slated to be placed in the Department of Radiology, will be utilized by several Institutes to carry out research protocols approved by an

NIH NMR Users Committee. Initial studies will be done at a magnetic field strength of **0.15** T and will include investigations of demyelinating disease, the effects of chemotherapy and radiation therapy on NMR parameters, and whether NMR can be used to predict patients' responses to chemotherapy and radiation therapy.

Cellular Metabolism.—A fifth NMR research group has been formed at NIH by Charles Meyers, Chief of the Clinical Pharmacology Branch of the Division of Cancer Treatment at the National Cancer Institute (NCI). This group will be exploring the use of NMR in the study of the metabolism of both normal and cancer cells, as well as the effect of various drugs on cellular metabolism. The group will also be exploring possible applications of NMR to the study of the development of tumors **(37).**

Meyers' group will be drawing on the expertise of Dr. Jack Cohen, an NIH veteran of 15 years, whose research has focused on biochemical applications of NMR. Over the past *3* years, Cohen has used NMR spectroscopic techniques to study cellular metabolism **(67),** proteins, DNA conformation (34), and drug binding, including the binding of the chemotherapeutic agent Adriamycin to specific DNA sequences. Cohen has recently developed a method to perfuse living cells in an NMR spectrometer *(68),* which he has used to study ATP metabolism in mammalian cells (Chinese hamster lung fibroblasts).

Extramural Research: Past

NIH-Supported NMR Spectroscopy Research Facilities.—Although a complete description of NIH-supported, conventional NMR spectroscopic research is beyond the scope of this report, mention should be made of a number of NIH-supported NMR-spectroscopy research facilities around the United States that are devoted to the study of biological molecules. These include the Middle Atlantic NMR Research Facility at the University of Pennsylvania, the Western Regional NMR Biomedical Facility at the University of Utah, the Stanford Magnetic Resonance Laboratory, the Purdue Biochemical Magnetic Resonance Laboratory, the NMR Facility for Biomedical Studies in Pittsburgh, and the Francis Bitter National Magnet Laboratory at the Massachusetts Institute of Technology **(190).** The MIT National Magnet Laboratory, run by Dr. Leo J. Neuringer, is a national resource that makes available high field NMR spectrometers to biomedical investigators.[2]

NMR Imaging.–Although a few of the NMR-related extramural grants that have been funded by NIH over the past decade have been funded by the National Heart, Lung, and Blood Institute (NHLBI) (e.g., research by Lauterbur in 1975 related to the use of NMR imaging to study blood flow and about **$200,000** per year provided to Lauterbur by NHLBI since *1978)* and other Institutes, most of them have been funded by NCI. The first extramural NCI grant related to NMR imaging was awarded to Lauterbur at SUNY-Stony Brook in 1973 after publication of his landmark article (115). The award was made to help Lauterbur further develop his technique of NMR imaging and investigate its application to cancer research. His initial funding of approximately $100,000 per year for *3* years has been renewed at an approximately constant level, without interruption, since 1973. NIH also supported early work on T_1 measurements of surgically excised human tumors (45,46) and tumors in mice and rats *(85,92),* as well as on the imaging of tumors in live animals *(44).*

Extramural Research: Present

NIH is currently funding approximately $2 million of research relating to NMR imaging and/or in vivo spectroscopy in at least *10* different institutions **(204).** A complete description of the content of this research is beyond the scope of this report. The Department of Energy has awarded an additional $1.8 million for NMR-related research (204). It should also be noted that in 1983, NIH began providing support for innovative research performed by small businesses in a program similar to the one sponsored by the National

[2]Of interest is the fact that IBM has recently supplied several million dollars to the Brigham & Women's Hospital in Boston, the University of California at Berkeley, and the MIT National Magnet Laboratory for a joint research program aimed at addressing basic biological and medical questions and developing a high-field, whole-body magnet with sufficient field homogeneity to permit performance of in vivo ^{31}P spectroscopy (1).

Science Foundation (197). No information was available regarding whether support has been provided for NMR research under this program.

Extramural Research: Future

The dramatic advances over the past decade in diagnostic imaging technologies, many of which can assist clinicians in diagnosing multiple types of pathologies, have created the need for comparative performance studies to clarify how our expanding diagnostic imaging arsenal can be used most effectively and efficiently. In October 1981, the NCI expanded its focus beyond supporting research directed principally at cancer detection and diagnosis by forming a Diagnostic Imaging Research Branch to advance the art of imaging all types of morphologic and functional pathologies.

In October *1982,* this Diagnostic Imaging Research Branch announced a solicitation of proposals (191) for the performance of studies: 1) to explore and define the current and potential usefulness of present-day NMR imaging systems in clinical applications; 2) to establish optimal imaging conditions for NMR use in specific clinical problems; and *3)* to carry out comparative performance and evaluation studies to determine the capabilities and limitations of NMR imaging systems in comparison with other modalities for clinical applications in human subjects in the detection, imaging, quantification, and diagnosis of morphological and functional pathology and in the noninvasive characterization of tissue (191).

The other techniques with which NMR is to be compared could include, but are not limited to, conventional X-ray imaging, computed tomography (CT), ultrasonic imaging, and radioisotope imaging, including single photon emission computed tomography (SPECT), and positron emission tomography (PET). Awards are to be for *3* years and are in the form of cost-reimbursement contracts. Announcements of awards, originally scheduled for June *1983,* were made in mid-1984 (144).

There were three minimum requirements for qualification for an award: award recipients must own or have available a working NMR-imaging system of sufficient size and image quality for meaningful whole-body or head studies of human subjects; recipients must have access to equipment to carry out comparative imaging with one or more of the other techniques listed previously; recipients must be capable of imaging at least 150 patients in the first year and at least 200 patients in each of years 2 and 3 (191).

NIH is also planning to issue a Request for Applications for grants to study the physical, chemical, and biological bases for T_1 and T_2 relaxation times to gain further insight into the information implicit in these parameters. Although a 3-year program, with up to $1 million in grants in the first year, is being considered, no funds have actually been approved (144).

NIH is also considering the possibility of funding a small number of training fellowships in NMR (144).

National Science Foundation

The National Science Foundation (NSF), an independent agency of the Federal Government that supports basic research in *18* different scientific subject areas, supported a pioneering research project in NMR imaging through its Research Applications Directorate (Instrumentation Technology Program) during 1977-79[3] as well as a 3-year ($95,000) project by Lauterbur related to microscopic NMR imaging. NSF currently has no programs that support research in NMR imaging per se. However, NSF has provided, and continues to provide considerable support for investigations relating to digital signal processing, two- and three-dimensional analyses and image reconstruction, as well as other scientific principles on which NMR imaging is based (49).

NSF Regional Instrumentation Facilities

In 1978, NSF initiated a program designed to improve the quality and scope of research conducted in the United States by making sophisticated instruments broadly available to researchers in both academia and industry (196). This program of Regional Instrumentation Facilities was predicated on two beliefs. First, there was thought to be a growing need for researcher ac-

[3]There was $309,500 awarded under grant #APR-7708185. "In-Vivo Nuclear Magnetic Resonance of Flow Patterns" to the University of California at Berkeley in 1977.

cess to the powerful scientific instrumentation that had evolved out of recent advances in electronics, but which unfortunately was affordable by only a few research institutions. Second, it was thought that a program of instrumentation sharing might encourage interaction and cooperation between researchers from scientific disciplines that do not ordinarily collaborate with one another *(150)*.

By November of 1979, NSF had awarded a total of $11,392,000 to eight universities in seven States for the establishment of such regional instrumentation facilities (196). Of the 14 grants awarded during the first 2 years of the program, 5 went to universities to establish facilities for the performance of high-resolution NMR spectroscopy, at a cost of over $5 million.[4] Researchers in these instrument facilities used the NMR spectrometers in a broad range of physical, chemical, biochemical, biophysical, and molecular biologic experiments. No NMR imaging instruments were installed in the facilities and no imaging research was performed. No information is available regarding the extent to which the spectroscopic research performed in these facilities was pertinent to the later development of NMR imaging techniques.

NSF also provides institutional support to the National Magnet Laboratory at the Massachusetts Institute of Technology.

Small Business Innovation Research Program

Although NSF directs most of its research support to basic scientific and engineering projects at academic institutions in the United States, since 1977 it has also operated a Small Business Innovation Research (SBIR) program. This program encourages science-based and high-technology small businesses with strong research capabilities in applied science, basic science, or engineering to submit proposals pertaining to research in scientific or engineering problems that could lead to significant public benefit (197). Three primary objectives of this program are to stimulate technological innovation in the private sector, to increase the commercial application of NSF-supported research results, and to increase the national economic and social benefits derivable from Federal research investments (197).

Awards under the most recent SBIR program solicitation were to have been announced in January 1984. Research proposals pertaining to: 1) the application of superconductivity to electronically oriented industries; 2) improved NMR probes; and 3) new procedures for NMR data display have been particularly encouraged. NSF expects to award about 100 Phase I (feasibility study) grants of up to $35,000 each. One-third to one-half of Phase I awardees will receive Phase II grants, which will cover 2 years of research and are expected to average $200,000 each.

NSF and ACR Research Workshop

In November 1982, NSF and the American College of Radiology (ACR) sponsored an engineering research workshop for engineers, physicists, computer experts, physicians, product developers, and business managers to identify critical gaps in imaging knowledge that require engineering support and to examine how engineering researchers, medical scientists, and clinicians could develop effective collaborative relationships out of which advances in radiological imaging might emerge *(49)*.

In addition to identifying areas in which basic imaging research is needed, the conference attendees addressed the current research and development roles of various elements along the research-development-production-application continuum. They concluded that the medical imaging-system manufacturers perform little of the basic research on which advances in imaging technologies depend:

> . . . The instrument producer functions largely as a designer/integrator of high technologies into functional systems, taking the knowledge resulting from research done elsewhere and converting it into clinically useful imaging systems (49).

The need for additional sources of support for basic research was underscored.

[4]NMR spectroscopy centers were established at Colorado State University, the University of South Carolina, the California Institute of Technology, the University of Illinois, and Yale University.

ENGLAND AND SCOTLAND

Between 1973 and 1983, at least three different noncommercial entities provided financial support for NMR research in England and Scotland. Between 1974 and 1979, the Medical Research Council, the British analog of our NIH, provided support to three different groups. Two of these groups were based at the University of Nottingham, one under the direction of Professor Peter Mansfield, the other under Professor Raymond Andrew. The third group was based at the University of Aberdeen in Scotland, under Professor John Mallard. Andrew's and Mallard's groups received support from the Medical Research Council between *1975* and 1978; Mansfield's group received support between 1976 and 1979.

In late 1977, the Wolfson Foundation, a private philanthropic organization in England, announced the availability of funds for medical research. Andrew's group at the University of Nottingham used funds received from the Wolf son Foundation between 1978 and 1980 to do NMR imaging research, including construction of a whole-body NMR imaging system.

Finally, the Department of Health and Social Security (DHSS) in England, through a program designed to support development of technology that might be of use in hospitals, also provided significant financial support for the development of NMR imaging technology. In *1976,* DHSS provided funds to help establish an NMR research team at the London-based company EMI *(29).* A resistive magnet-based machine was built at EMI and head images were produced in *1978 (29).* Following 2 additional years of developmental research, the EMI team constructed a superconducting, whole-body NMR imaging system, which was installed in Hammersmith Hospital in London in March 1981 (29). EMI also contributed funds to this development project. '

In 1981, NMR imaging began at the Hammersmith Hospital using the resistive NMR unit developed by EMI. DHSS apparently has also provided support to the clinical imaging program at Hammersmith, as well as support for NMR research to Professor Mansfield at the University of Nottingham (177).

'In approximately 1977, GEC of England independently began work on the development of an NMR imaging system. In April 1981, GEC acquired the Picker Corp. and formed Picker International by consolidating the Picker Corp., GEC Medical, and Cambridge Medical Instruments. In October 1Q81 Picker International Ltd. Division in England purchased EMI's NMR technology and program, including its program at Hammersmith Hospital

RESEARCH AND DEVELOPMENT POLICY ISSUES

Certain differences between the history of the development of NMR imaging in the United States and Great Britain should be considered. In contrast to the NSF program's supporting basic research by small businesses on a broad spectrum of scientific and engineering problems (as opposed to product development research), the British Government attempted to develop technology that might specifically be of use in hospitals. This effort was focused through a program funded by DHSS that lent considerable financial support to the development of NMR imaging techniques. Comparatively little support for the specific development of NMR imaging technology was provided by the U.S. Government. However, once it became apparent that the development of NMR imaging systems was not only commercially viable, but also potentially extremely profitable, U.S. manufacturers rapidly and intensively began investing in NMR imaging development programs. In addition to applying their considerable electronics and engineering resources to this effort, U.S. manufacturers aggressively (and successfully) recruited scientists who had been actively involved in the early NMR development programs in British universities. Similarly, U.S. universities and hospitals have recruited British NMR scientists to help initiate and promote active NMR imaging research and development programs, contributing to what has become somewhat of a "brain drain" from Britain.

Finally, in Britain there seem to have been several groups of physicists based in university settings who had background and interest in the development of NMR imaging techniques and who interacted and collaborated with medical researchers, clinicians, and each other. In the United States, in contrast, most of the early work on NMR imaging was done by Lauterbur and Damadian with apparently little, if any, interaction between the two, despite the fact that both were at SUNY campuses. In addition, there seem to have been fewer centers in the United States in which scientists with varied backgrounds collaborated on the type of interdisciplinary research that resulted in the NMR imaging advances in Britain. Perhaps the collaborations between physicists and physicians that are now developing as part of hospital- and university-based NMR imaging programs, as well as the recognized need for interdisciplinary research collaborations that emerged from the *1982* NSF and ACR research workshop, will change this situation in the future.