ALL SCIENCE IS INTERDISCIPLINARY – FROM MAGNETIC MOMENTS TO MOLECULES TO MEN

Nobel Lecture, December 8, 2003

by

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The title is not a tribute to some trendy hybrid field, but an introduction to a lecture on a Nobel Prize for Physiology or Medicine that is shared by a chemist and a physicist.

Few events could illustrate more clearly the blending both at the boundaries, and sometimes through the bodies, of our disciplines. For that is what they are, disciplines, not natural categories with rigid boundaries to be defended against intrusions, but guides to instruction and efficient administration.

Historically, the record is clear. Chemistry, for example, was cobbled together from mystical alchemy, metallurgy, physics, mineralogy, medicine, and cookery, eliminating incompatibilities as it evolved and consolidated into a more-or-less unified discipline. Physics has been formed, and enriched, by contributions from astronomy, mechanics, mathematics, chemistry, and other sciences. We have recently observed the rationalization of much of biology by chemistry, with the help of physics.

Nuclear magnetic resonance began within physics, at a confluence among particle physics, condensed matter physics, spectroscopy, and electromagnetics. Discovery of ways to observe the subtle properties of atomic nuclei in solids, liquids, and eventually gases, earned Felix Bloch and Edward Purcell a Nobel Prize in Physics in 1952. Applications to studies of molecular motions and structures began almost immediately. The discoverers themselves, it is told, even used their own bodies as samples. In an early predecessor to MRI, Jay Singer measured blood flow in a human arm, and actual medical measurements were started when Erich Odeblad, a Swedish M.D., constructed apparatus and devised methods to study very small quantities of human secretions for medical purposes. Other biological studies followed, in other labs, using animal tissues, including hearts, and entire small animals.

In 1971, Raymond Damadian observed that some malignant tissue, obtained from implanted tumors removed from rats, had longer NMR relaxation times than many normal tissues. This observation caught the attention of several people, and Hollis decided to attempt to confirm and extend it by a study of a related system, Morris hepatomas in rats, readily available to him at Johns Hopkins University. At one point, a post-doctoral fellow in his labo-

ratory, Leon Saryan, brought some of the animals to the small company in western Pennsylvania which had actually carried out the earlier Damadian work. There, the rats were sacrificed and dissected and the tissue samples studied by NMR. I happened to be present to observe the entire process, for reasons described elsewhere, and, as a chemist not ordinarily involved with animal experiments, found them rather distasteful. All such NMR experiments were subject to error from non-uniformities in sample composition, the static magnetic field, and the radiofrequency magnetic field. However, the differences in the NMR signals from one tissue to another, normal as well as diseased, seemed robust in the experiments I observed. I thought they might actually be reproducible and useful, especially if the signal intensities, relaxation times, etc., could be measured from outside the living body with sufficient spatial resolution.

That evening, over dinner, it occurred to me that, as the frequencies of NMR signals depended on the local magnetic field, there might be a general way to locate them in a non-uniform magnetic field. I knew, however, that a static field could not have a unique value in each location in three dimensions, but that a complex shape could be represented by an expansion in a set of functions such as those provided by the correction, or "shim" fields, available on NMR machines to cancel unwanted magnetic field non-uniformities, term by term, with linear gradients, quadratic ones, etc. Could this be the answer? A little reflection made me doubt it. I recalled that single-center expansions of molecular wave-functions had been tried in quantum chemistry, but converged on useful solutions slowly and poorly. An alternative occurred to me. What if one used a large set of simple linear gradients, oriented in many directions in turn in three dimensions? I knew of no examples in any field. This was early September 1971, and X-ray CT was not yet widely known, and neither had I encountered the similar ideas that were being tested in radioastronomy by Braceewell and in electron microscopy by Herman and Gordon, and by others in different fields. Nor did I know of any mathematics to solve such problems, but I recalled another idea from quantum chemistry, that when equations were not solvable in analytic form, an iterative method, in which approximate solutions were compared to known properties and systematically adjusted to a closer and closer fit, could be used.

To test this idea, I wrote down small arrays of numbers such as 1s and 0s, in small arrays 4×4 or even 8×8 square, and added them along the vertical and horizontal directions, representing the 1-dimensional data that would be generated by linear magnetic field gradients perpendicular to those directions, as well as data, at 45° and 135°, that could be generated similarly. The "data" could then be "back-projected" across the image space as a series of bands and summed where they crossed, from which the trial image of summed intensities could be projected in each of the original directions for comparison with the actual "data", and modified by added or multiplicative terms to agree with it. The procedure might then be repeated, in hopes that the next computed trial image would be a closer approximation on each cycle to the synthetic original one. I asked local mathematicians whether such a procedure

was known and would work. All said they knew of no examples, and some said it was obviously valid, while others said it was clear that it would not converge, so I just tried it myself, with pencil and paper calculations. The result, with such simple mathematical "phantoms" (test objects) at least, was that the calculations converged very rapidly indeed. Later, a computer scientist with whom I had consulted came across a paper in a subsequent issue of a journal that used exactly my algorithm. This simultaneously validated the method and eliminated my claims to priority. I later learned that much work on the so-called "reconstruction from projections" problem had been published, by many people in many contexts, in recent years, almost all developed independently in different fields. My real interest, however, was in the magnetic resonance imaging problem, and that remained unique.

I then turned my attention to the question of whether there would be enough NMR signal-to-noise ratio with large enough radiofrequency coils to surround a human body and the low magnetic fields I thought might be practical in resistive magnets over such large volumes. The standard reference, "Nuclear Magnetism", by Abragam provided equations that suggested that the answer was favorable. At about the same time, my review of the magnet literature revealed that resistive magnets with fields of the order of 1000 gauss (0.1 tesla) and diameters of about 1 meter could be constructed and operated economically with enough field uniformity to support the NMR experiments I had in mind.

It then appeared that all the requirements could be met if the right research and development could be done, so that a new and useful medical diagnostic tool would be available. But first, there was another matter to resolve. A patent attorney at the company had advised me to do no experiments at my university, as they would compromise my patent position. He and I had been actively working on preparing patent application documents, in exchange for his fee of a percentage of any financial returns that might result. Unfortunately, a business dispute developed between us in connection with the company, and he declined to continue with our agreement. When that happened, I made a patent disclosure to my university, which in turn sent it to the organization they used to evaluate such documents and prepare patent applications.

In the meantime, I began experiments, preparing test objects by attaching 1 mm diameter glass melting point capillaries to the inside of 5 mm glass NMR sample tubes, the capillaries filled with ordinary water (H_2O) and the outer tubes with heavy water (D_2O). The reason for the D_2O was to roughly match the magnetic susceptibility across the sample so that the capillary signals would be less distorted than they would have been with air in that space. I first tried three capillaries, but the signals were too complex for easy interpretation, so I tried just two. I also tried using the linear gradients in the magnetic field supplied by the appropriate "shim" controls on a small analytical NMR spectrometer in the Chemistry Department, with 5 mm sample tubes filled with ordinary water. As expected, their projections were half-ellipses, or semi-circles for the proper adjustment of the strength of the gradient. For an actual test of the image mathematics on real data, I attached a paper disc,

marked at intervals of 45°, to the outer tube containing two capillaries and rotated it to orientations of 0°, 45°, 90° and 135° relative to the gradient direction while recording the NMR signal on a pen and ink recorder. I then digitized the recordings by measuring the height of the curves at intervals with a ruler and recording the numbers on a piece of paper, with the intervals corresponding to the projections of a square grid at each angle. The numbers were then transferred manually to punch cards that could be fed to a reader attached to the departmental instrument control computer, originally intended only to operate an X-ray diffractometer for single crystal structure determinations. Its memory (ferrite cores) was so limited that all calculations had to be made in integer ("fixed point") mode, and intermediate results had to be punched out on a deck of cards to be reentered later for the next step, and each subprogram had to be kept on a separate deck of punched cards. The final result was then printed by a typewriter as a 20x20 array of numbers, and the "image" produced by hand-drawn contours on that array. This seems tedious on later description but was exciting then because the whole process and its results were being encountered for the first time, especially as I recognized that the "pictures" were a new kind of image, based on principles completely different from those behind other imaging methods. To emphasize this point, I coined the new word "zeugmatography" as a description, checking with a classical scholar for its fidelity to ancient roots and with a speaker of contemporary Greek to ensure that the meaning of "zeugma" had not shifted during later centuries.

Reassured, I used it in a manuscript I wrote for the journal *Nature*, which was summarily rejected. I felt this was a mistake, not because I foresaw all of the medical applications that would follow, but because of the physical uniqueness of the concept. I was also trying to think of another example that would work in practice, but it was to be over a quarter of a century later that an example, involving the differential shift of the spectra of two closely-spaced atoms by an inhommogeous electric field, was published, but the authors did not notice the similarities. My appeal to *Nature* was followed by submission of a revised version of my manuscript containing references to cancer and other more obviously relevant topics, and this time it was accepted. Almost thirty years later, *Nature* publicly celebrated its appearance there. Slightly earlier, I had presented my results in a short contributed paper at an American Physical Society meeting, which then had a policy of accepting any meeting talk by a member, but it was attended by only a handful of listeners, one of whom was a graduate student who told me that his professor had done the same thing, but I never found any evidence that he had. A similar pattern repeated itself several times in later years, with people telling me that they had the same ideas but had not followed them up with experiments and publication.

This work, and its subsequent elaborations, became the subject of my lectures afterward at most meetings I attended, including seminars. Before I began describing it in detail everywhere, however, the University's agent rejected the patent application because they felt that it could not generate enough

funds to pay for the application process. I then asked my university for permission to pursue the application independently but never received a reply. I was not in a financial position to quit my job and defy the university, and the grace period for applying for a U.S. patent after publication had nearly expired, so I abandoned that idea and decided instead to encourage others to pursue this new technology, inviting everyone interested to visit my laboratory to observe our efforts and learn from us. People did come, from industry, academia, and government laboratories, foreign and domestic, and I began supplying a bibliography of such work to all and helping to organize meetings on the subject to compare our methods and results. Among these were Professor Raymond Andrew and members of his group at Nottingham University, and Drs. Mansfield, Moore, and others there, as well as representatives of medical instrument companies and medical doctors and medical physicists themselves. As I hoped, interest began building as many other groups were involved.

We continued our work, which shortly involved graduate students and postdoctoral fellows as well as undergraduate research students, and, as I had hoped, more contributions were published by other laboratories, with some remarkable early images from Waldo Hinshaw in Andrew's group at Nottingham. As the depth and breadth of application grew, both large and small companies began to see opportunities, and within less than ten years commercial instruments began to come to market, large enough to hold a human being and to support true clinical research. Competitive pressures among physicians, industrial interest, and multiplying applications and techniques began to generate the explosive growth that was to characterize the past twenty years, leading, among other things, to the recognition of this phenomenon by the Royal Swedish Academy of Sciences. I and my group continued to make contributions through this period as well, some of them significant, but the most gratifying experiences emotionally were those when a stranger would volunteer "you saved my daughter's life", or "your machine saved me from an unnecessary operation". By the end of the millennium, despite the continuing excitement of the field, almost thirty years of a detour from chemistry to medical imaging began to pall, and I changed my focus to a field of chemical research, just in time for my past to catch up with me in the form of a Nobel Prize. All detours should be so productive!

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