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Perspectives in Magnetic Resonance

Beginnings and early history of the International Conferences on Magnetic Resonance in Biological Systems: Development of the basic ideas in the field

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ABSTRACT

The early history of the principal meeting in the field of biological NMR spectroscopy, the International Conference on Magnetic Resonance in Biological Systems (ICMRBS), is presented from the perspective of one of the founders.

The idea of organizing a meeting of those who began applying magnetic resonance techniques to biology did not arise under the most promising circumstances. As early as 1958 distinguished chemists were arguing that there was nothing new to be discovered by this technique and the Gordon conferences on Magnetic Resonance in Chemistry should be discontinued. Representatives of Varian Associates, who at the time still held the Bloch patents and a virtual monopoly on NMR instrumentation were saying that the market was saturated with their A60 and nothing new was worth developing. Not much progress was being reported on biochemical applications since the first protein – ribonuclease – spectrum was published in 1957 by Saunders, Wishnia and Kirkwood, and accounted for in terms of its constituent amino acid spectra by Christine Jardetzky and myself. The main obstacles to meaningful biological applications were eminently clear: the low sensitivity and low resolution of the method.

Still a Gordon Conference was held in 1963, and on one of the afternoons Mildred Cohn, Richard Ernst and I were sitting under a tree overlooking Webster lake, trying to assess the situation. We had just reported the first experiments on NMR signal averaging [1] using the relatively simple Computer of Average Transients (CAT) originally developed for neurophysiology, which yielded a roughly 50–100-fold improvement of sensitivity. This was important, because biochemical reactions involved concentrations far below the standard sensitivity of the NMR instruments.

Contemplating the matter Richard Ernst suggested that the averaging might be much faster if it were done in the time domain, the final spectrum to be obtained by a Fourier transform of the summed free induction decays (FID). This immediately made sense, since an FID could be collected in most cases of interest in 30 s or less, whereas a single continuous wave spectrum was taking several minutes and the average several hours. There was some question, as to whether the mathematical operation could be carried out fast enough on contemporary computers to make a real difference. In the original version, the FID data had to be punched on cards to do a Fourier transform. But we all shared the hope that faster computers were within reach.

This was of course the basic idea on which all modern spectroscopy now rests. A warm and colorful account of the above and subsequent conversations which led to it has already been recorded for posterity, with pictures, by Richard Ernst [2]. In retrospect it is difficult to believe that it took Ernst and Anderson 2 years to get their experimental realization of this idea into print [3], and it took 6 years, before the first Fourier transform spectrometers appeared on the market. In the meantime continuous wave CAT NMR spectroscopy became the standard method of sensitivity enhancement, with minor variants, coyly called the DOG and the MOUSE method.

By the evening, the conviction that we were likely to have a future was sufficiently firm that Mildred Cohn, Bob Shulman and I agreed to form an organizing committee, which later included Terry Eisinger and Irv Isenberg, to plan a 1964 meeting devoted to biological applications of magnetic resonance. To put together a program for such a meeting however did not prove to be a simple task. It would hardly have been appropriate to call a meeting just to have everyone listen to the three of us, but NMR work centered on biological or biochemical problems – with one or two isolated exceptions – did not exist outside of our laboratories. Electron Spin Resonance (ESR) in biology was at the time receiving much more attention. No lesser a light than Albert Szent-Gyorgy (1935 Nobel Prize for the isolation of vitamin C) had proposed that the energy of muscular contraction was transmitted by free radicals. Harden

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McConnell and I carried out a series of careful, never published ESR experiments during muscular contraction, but failed to detect any free radicals in the process. Nevertheless the level of enthusiasm for invoking free radical mechanisms in a variety of biochemical processes, from DNA replication to aging was still very high. The field also presented a political problem. Its most vocal proponent at the time was Barry Commoner, future candidate for President of the United States, who was equally well known for his radical political views. This led to frictions and considerable confusion. When he was invited by the Chemistry Department of the University of Minnesota and announced the title of his ESR seminar as "Free Radicals in Biology", the Department Chairman received a call from a member of the Board of Regents, reminding him to keep politics out of academic life.

One of the aims of the meeting was to interest serious established scientists – especially biologists and biochemists – in the potential of the still unknown method. Fortunately some of them – Charles Townes, Britton Chance, Norman Davidson, Martin Kamen responded with enthusiasm and later offered astute philosophical remarks as session chairmen.

So a meeting patterned on the Gordon Conference model was held July 20–22, 1964 at the American Academy of Arts and Sciences in Boston. It proved to be the first of a rather successful series of biennial meetings now numbering over 20. Attendance was limited to 100 participants and, to our surprise there was sufficient curiosity and enthusiasm so that the limit was easily reached. Not more than 30 of the 100 had actually touched – or even seen – a magnetic resonance spectrometer. When one now attends these meetings along with over 1000 experts one can see how science and times have changed.

An account of the Boston meeting was published in Science [4]. Applications of NMR at the time were limited to the study of the structure and conformation of biologically interesting small molecules – amino acids (Fujiwara), pentoses and hexoses (Lemieux) and molecular complexes – metal-ions with porphyrins and nucleotides, notably ATP, often using a combination of NMR and ESR (Schulman, Eisinger, Feher, Vänngard) and the use of relaxation to study complexes of proteins with small molecules (Jardetzky and Fischer) or water (Berendsen), or for the study of the kinetics of biochemical reactions (Mildred Cohn) (Fig. 1). Several observations that were the first of their kind, though not studied in detail, were also noted and discussed – the observation of a contact shift in cytochrome C by Art Kowalsky, or the C2 histidine peak in ribonuclease by Morton Mandel.The number of ESR applications was larger, including metal-ion–flavoprotein complexes (Beinert), metal-ion – ceruloplasmin complexes (Malmström and Vänngard) and the attempts at a differential diagnosis of medical and surgical jaundice by ESR (Commoner). Nevertheless the general conclusion could be reached that NMR was providing and was likely to provide a larger share of definite, generally applicable answers that would stand the test of time, while the very heated controversies about the meaning of ESR observations "left one wondering whether the overabundance of enthusiasm and technical know-how of the... pioneers in this area is really sufficient to cope with the very real handicap posed by the lack of uniquely identifying characteristics in most of the signals observed".

During the last session the question was put to a vote whether another meeting on this subject should be held. The vote was a unanimous yes, and so the discussion shifted to questions of where and when. Most felt that a meeting in 2 years was more appropriate, given the slow rate of progress in the field. On the question where, opinions varied widely. Some favored a continuation of Boston meetings under the same management. Some of us felt that the meetings should become international, so that everyone would be exposed to work and philosophy of science in different cultures. For this we were angrily berated by Barry Commoner: "You are advocating junkets" he said, "this is not what science is about. There is no significant work in this field outside of the United States. The meeting should stay in the United States." A compromise was reached by conducting an opinion poll after the meeting, that meetings would alternate between the US and foreign countries.

Fig. 1. Oleg Jardetzky and Mildred Cohn at the first ICMRBS in Boston, Massachusetts, USA 1964.

The issue was resolved, when the Swedish group – Ehrenberg, Malmström, Vänngard – proposed to organize a similar meeting in Sweden in 1966. Except for Barry Commoner no one objected and the decision was made to accept the Swedish proposal.

The second International Conference on Magnetic Resonance in Biological Systems was organized as a Wenner-Gren Symposium under the honorary chairmanship of Hugo Theorell, and held in Stockholm June 9–15 1966. It is so far one of only two meetings for which the papers presented were published in full as an independent book [5]. It was a small meeting – fewer than 100 participants and it dealt mostly with applications of Electron Spin Resonance. The most significant contribution of NMR studies was the detailed description of the proton relaxation enhancement method for the study of enzyme mechanism by Mildred Cohn, which she had developed. For enzymes which can be activated by a paramagnetic ion bound to the active site, such as pyruvate kinase and other phosphotransferases, it is possible to estimate the number of water molecules in the coordination sphere of the ion, their exchange rates and the ion binding constants by measuring the chamges in the solvent water relaxation time at different temperatures and ion concentrations. The kinetics of the enzyme reaction can also be followed, since all of these parameters change in the process. Particularly noteworthy were the first protein spectra using superconducting magnet technology – the Varian 220 MHz spectrometer – presented by Bill Phillips. As expected, they showed a perceptible improvement over the then prevalent 60 MHz spectra, but not enough to allow extensive assignments in biological macromolecules.

The third ICMRBS was organized by W.D. Phillips and C.C. McDonald at the Airlie House in Warrenton, VA, October 14–18, 1968. It was still a meeting with fewer than 100 participants, but there was a strong feeling of curiosity, excitement and optimism

in the air, akin to the exuberance reported by early pilots at takeoff. The first results of Fourier NMR were reported, not by Ernst, but by Mel Klein. Mel Klein was a pivotal figure in the early days of NMR, highly respected not only for his experimental ingenuity and remarkable critical judgment as well as a rare sense of fairness, but also for his sincere disdain for public attention and recognition. Many a seminal experiment he had done remained unpublished until it was published by someone else. My Ph.D. thesis, published in 1956 as the first NMR study of the sodium ion and its complexes with biological molecules and hailed by Paul Boyer, who accepted it for publication in the Archives of Biochemistry and Biophysics, as ''the beginning of biological applications of NMR" was a good example. Only a year later I found out that Mel Klein had done pretty much the same experiments at the same time or even earlier – and never published them. The introduction of signal averaging provided a second example.

Donella (Dee) Meadows from my laboratory reported on histidine assignments in ribonuclease, which allowed her to predict the orientation of such inhibitors as 2′, 3′ and 5′ CMP in the enzyme binding site which had just become known from the crystal structure determinations by Richards and Wykoff. Subsequently confirmed many times by X-ray diffraction, this was really the first demonstration that significant structural information on proteins could be obtained by NMR. Although she did obtain her Ph.D. from Harvard in 1969, Dee chose not to pursue a scientific career, bur a few years later became more famous than the rest of the NMR community combined as the author, with her husband, of the book ''Limits to Growth" a computer model study supported by the Club of Rome, which predicted ecological disaster from the rates of population growth and consumption. It was translated into 34 languages and rattled the Economics community. Sadly, she died relatively young in 1999.

Bill Phillips presented a detailed NMR study of lysozyme denaturation. Following the disappearance of the upfield shifted methyl resonances as the temperature was raised, the main conclusion was that denaturation was a transition between two states, as generally thought at the time. However in the discussion several other changes in the spectrum were noted, which although not yet characterized, raised the hopes that NMR may be a method for the detection of intermediate states in protein denaturation. Jack Cohen pointed out that the ordinary thermally ''denatured" state of lysozyme is in itself an intemediate state, since complete random coil configuration – i.e. complete denaturation can only be obtained by reducing all disulfide bonds in the protein.

Bob Shulman summarized his extensive studies of heme proteins, reporting a number of assignments of contact-shifted heme resonances, temperature dependence studies which excluded the possibility that one was dealing with ring-current shifts, and the answer to the main question posed in the study: the nature of the phenomenon that had been known as ''heme–heme interaction". Although oxygenation of one heme in hemoglobin facilitates the oxygenation of the next (hence the term heme–heme interaction), the facilitation results not from a direct spectroscopically detected influence of one heme on another, but from conformational changes of the main polypeptide chains. As Bob liked to put it ''the heme–heme interaction does not exist".

Mildred Cohn and Al Mildvan presented further results using the proton relaxation enhancement method, now including observations of enhancement in the spectra of substrates or inhibitors in rapid exchange.

John Markley, also from my laboratory presented preliminary results of his experiments on the simplification of the spectra of staphylococcal nuclease by selective deuteration, which also allowed some assignments and were beginning to yield information on the structure of nucleotide complexes. Protein deuteration experiments, although without selectivity and structural studies had also been reported by Crespi and Katz. Together these studies opened up the now blossoming field of isotopic spectral editing, an indispensable tool in modern protein structure determination. John also presented the first example of sequence-specific assignment by comparison of point mutants. His spectra showed four histidine C2 peaks, while the squence published by Chris Anfinsen's group contained only three histidines. Chris stood behind the quality of his sequence determination and we insisted that NMR cannot be wrong.The puzzle was resolved and both findings turned out to be correct. The sequence was done on the V8 strain and the spectroscopy on the Foggi strain of the nuclease. The latter contained a histidine in position 124, while the former did not.

The vote of the participants to continue these meeting was unanimous.

The fourth ICMRBS was organized by Rex Richards, E. Morton Bradbury and H.A.O. Hill at St. Catherine's College in Oxford, August 26–September 2, 1970. It was the last small meeting in the series. The program was very much in the spirit of the Airlie House meetimg. Morton Bradbury clarified the observation of two peaks in the helix–coil transition of amino acid polymers. Some authors had interpreted this finding as meaning the existence of two stable states, with infrequent exchange, while others seeing more cases with a single peak moving in the course of the transition, as in rapid exchange, believed the two peaks to be a result of polydispersity. Bradbury and his group presented convincing evidence that the latter interpretation was correct. Bill Phillips, Bob Shulman, Mildred Cohn and I presented more detailed results using our respective methods – high field (220 MHz) NMR of proteins and nucleic acids in Bill's case, further analysis of contact shifts in heme proteins by the Shulman group, proton relaxation enhancement studies of enzyme mechanisms by Mildred and stuctures of enzyme–inhibitor complexes in selectively duterated staphylococcal nuclease in my case. Another set of enzyme–inhibitor complexes for lysozyme was reported by Michael Rafferty and separately by Brian Sykes. An innovation was the participation in the meeting of a theoretician, Alberte Pullman, who had published a series of papers explaining the chemical shifts in biological molecules with quantum–mechanical models. Chemical shifts, which allowed an acurate definition of the covalent structure of molecules were proving too sensitive to define structure when non-covalent interactions were involed – as in the complex folding of biological macromolecules. The question of the best way of defining precise geometric parameters – notably internuclear distances – in such systems was very much on all our minds. Harden McConnell and coworkers introduced one method of obtaining long distance constraints – by attaching a stable free radical (spin label) to the macromolecule and estimating the distances from the relaxation enhancement on identified distant protons within the structure. In principle internuclear distance between neighboring protons could be estimated from the cross-relaxation effects (Nuclear Overhauser Effect) between them, provided the correlation time was known. The complete set of such distances would allow the complete definition of the macromolecular structure. When I said this, Harden McConnell cried ''this is an exaggeration!". The exchange is recorded in the proceedings of the Ciba Foundation symposium held in London earlier the same year, but the debate continued at the Oxford conference, with many participants doubting the feasibility of such an undertaking. Nevertheless, it was generally accepted that significant structural information – beginning with partial structures of binding sites and their complexes – could be obtained by NMR. As Gordon Roberts and I wrote in our review for the Advances in Protein Chemistry following the meeting – there was little doubt that NMR could be used as an independent method for protein structure determination, provided the difficult problems of poor sensitivity and resolution, and assignment are solved. A decade later, they were.

Oxford was by then also the home of Oxford Instruments, founded by Rex Richards and associates and producing superconducting magnets for spectrometers operating at 270 MHz. A first glance at protein spectra obtainable at this frequency showed the expected incremental improvement in resolution, still falling short of what would be needed for a complete analysis of the spectrum.

This was also the first meeting at which a formal organization was proposed. The organizers of the first four meetings met one evening at the home of Rex Richards and decided not to form a society but to give just enough formal structure to an essentially informal organization to ensure that it could function and provide continuity for the meetings. The meetings – to be known as the "International Conference on Magnetic Resonance in Biological Systems" (ICMRBS) were to be held every 2 years and organized under the auspices of the International Council on Magnetic Resonance in Biological Systems (ICMRBS). The Council would entertain proposals for the next meeting from different countries, appoint the Organizing Committee and choose the site for the subsequent conference. The Council would consist of (no more than) 15 members – three from each of the preceding five meetings – so that the term on the Coumcil would be 10 years, with the chairman of the oldest meeting serving as chair of the Council for the last 2 years on the Council. The Council would meet every 2 years during the Conference, at which time the organizers of the current meeting would join the Council, and the organizers of the oldest meeting would retire. The Council would not be a legal corporation and would not have a budget. (This provision was changed 20 years later.) All fund raising and management was to be handled by the current organizing committee and the sole responsibility of the Council was to audit the conference budget and to encourage all organizers to pass on some seed money to the next conference. Each Organizing Committee was to have complete freedom in shaping the program, with no interference from the Council. I was allowed to be the first chairman of the Council, to serve until the 1974 conference, (no one doubted that there would be one, even though no one thought about it yet) and as such I recorded the Oxford decisions on a piece of paper, which became a kind of Charter for ICMRBS. Looking at it at the time of this writing I realize with amazement that the organization has pretty much held up for 40 years.

The fifth ICMRBS was held at the Waldorf-Astoria Hotel in New York December 4–8, 1972, jointly with a symposium on "Electron Spin Resonance and Nuclear Magnetic Resonance in Biology and Medicine" of the New York Academy of Sciences, organized by Sigmund Lasker and Paul Milvy. It was the first large meeting – with over 500 participants, and the second and last to have its proceedings published later as a collection of full papers in a separate volume [6].

By then it was evident that several different approaches to the use of magnetic resonance in biological research had emerged, reflecting very different philosophies and that several different interest communities had formed. The major division in the NMR community was between those who were striving to develop comprehensive structural studies, cognizant of the fact that NMR was one of only two physical methods which could provide detailed structural information at atomic resolution (the other being X-ray diffraction) – and those choosing to use NMR as a probe method, like any other spectroscopic tool, using the resonance of a single group (akin to a chromophore), to draw conclusions about structure and processes in its environment. ESR of course could only be used as a probe method.

All types of biological structures had at least been looked at and reported at this meeting.There were extensive structural studies of nucleic acid building blocks by Maurice Gueron, P.O.P.Ts'o and their coworkers, a study of transfer RNA structure by David Kearns, Bob Schulman (Fig. 2) and coworkers and a study of histone binding to DNA by Morton Bradbury and coworkers. ESR studies by A.Ehrenberg, A. Müller and others dealt mostly with radicals formed as a result of radiation damage. There were many reports on proteins, especially heme proteins from the groups of Bob Schulman and Chien Ho, the allosteric transition in hemoglobin studies by Raftery and Huestis, and using spin labeling by Ogata and McConnell. A preliminary study of myoglobin and hemoglobin by electron–nuclear double resonance (ENDOR) was reported by George Feher, trying to extract structural information with only partial success.

The most dramatic presentation on protein NMR was a paper by Ian Campbell, Chris Dobson, R.J.P. Williams and A.V. Xavier from Oxford, entitled: "The determination of protein structure in solution: Lysozyme". Using paramagnetic (lanthanide) ions as shift reagents, they calculated the distances of several shifted residues from the ions on the basis of relaxation measurements. The paramagnetic probe method for protein structure determination was strongly championed by Williams and the Oxford group for several subsequent years, but it was found to have too many uncertainties, the cytochrome structure published in Nature [7] proved to be wrong and the method was eventually abandoned. The reasons for the failure of the paramagnetic probe method were discussed in detail in the later monograph by Jardetzky and Roberts "NMR in Molecular Biology" [8]. But at the time of the New York meeting it emphasized the hope of achieving a complete protein structure determination, a hope expressed at the meeting by only two other studies – our further progress report on selectively deuterated staphylococcal nuclease and as a parallel for nucleic acids the Kearns – Schulman investigation of transfer RNA.

There were numerous reports on the NMR structures of amino acids, small peptides, sugars and nucleotides and small molecule–protein interactions. Two attempts to examine model membranes by NMR one by Mel Klein, the other by Sunney Chan and their coworkers and a rather rigorous study of lateral diffusion in membranes using spin labeled lipids by Devaux and McConnell.

Of the major developments which were to play a key role in shaping the future of biological applications of magnetic resonance, and which were known to be occurring at the time, only one was discussed at this meeting. Maurice Gueron's presentation of nucleoside structure included a very detailed discussion of the Nuclear Overhauser Effect (NOE) and its use for determination of internuclear distances. The use of NOEs for this purpose had been known and discussed for some time, but the accuracy of the distance calculated from them, which depended on the accuracy of the correlation time used in the calculation, remained controversial. Although much evidence has been accumulated that good approximations can often be made, the basic problem remains: the internuclear distances calculated from NOEs are only as accurate as one's guesses about the applicable correlation times, even though relatively small errors in distances result from relatively large errors in correlation times because of the sixth power relation.

The proposal of Jean Jeener, made in 1971, to develop multidimensional NMR, although known to some of the participants from private discussions, was not mentioned at the conference. Ted Becker's review of recent progress in Fourier Transfer NMR dealt mostly with issues of water suppression.

Paul Lauterbur was not present at the conference and there was no discussion of the potential of NMR imaging, although his paper on zeugmatography appeared in Nature only a couple of months later [9]. Raymond Damadian presented extensive data on human and mouse tumors showing that the water relaxation time was longer in malignant than in normal tissues and proposed the use of relaxation measurents as a diagnostic method for cancer. There was no mention of imaging. The mechanism of this phenomenon remained unclear throughout the discussion, but was later clarified in the careful studies of Don Hollis [10]. The lengthening of the

relaxation paralleled the increase in the water content of the cell. It was not an indicator of malignancy per se, but only insofar as malignant cells, as all rapidly multiplying cells, frequently contained more water. All other presentations in the sessions on potential clinical applications of magnetic resonance dealt with the detection of free radicals by ESR as a diagnostic method for various conditions, none of which have stood the test of time.

The sixth conference in the series was organized by Kurt Wüthrich, Richard Ernst and Joahim Seelig in Kandersteg, Switzerland, September 16–21, 1974. In theory it was an attempt to return to the Gordon Conference format, but not quite successful, because attendance was well over 100.

A highlight of the meeting was the first detailed discussion of two-dimensional NMR spectroscopy by Richard Ernst. The ultimate importance of the method was by no means clear to anyone in the audience, but the fact that coupling constants could be resolved and separated did raise the hope that the problem of resolution could be solved.

There were the by now customary progress reports on the use of the proton relaxation enhancement, contact shifts in heme proteins, selective isotopic labeling and structural studies of small peptides and enzyme bimding sites. At the center of attention were the efforts of the Oxford group led by R.J.P. Williams to use lanthanide shift reagents for a complete protein structure determination. An impressive number of distances were identified in lysozyme, in agreement with the crystal structure which had been known for some time. Yet skepticsm about the generality of the method prevailed, because of the basic problem of extrinsic paramagnetic probe methods – the possibility that one had to deal with multiple binding sites. A fair amount of imterest was generated by protein spectra obtained on the first 360 MHz spectrometer installed at Stanford in 1973.

Represented in the program by a poster, but extensively discussed was Willie Gibbons' combined use of coupling constants and NOEs to obtain complete assignments in gramicidin S, which was published 2 years later. The generality of the method was immediately clear, but no one was ready to believe that resolution could be sufficient to make it applicable to larger protein structures. And yet, this Gibbons paradigm, as I called it in later papers (for a summary, [11], became the basis of the sequential assignment method developed by Wüthrich and Wagner in the late seventies.

More as a curiosity than a major advance was viewed Paul Lauterbur's presentation of a reconstructed image of a green pepper. Rex Richards gave a lecture on the work of the Oxford group examining ^{31}P spectra of metabolites in intact tissues (“in vivo NMR"). A round table discussion involving Anders Ehrenberg, Paul Lauterbur and Robert Schwyzer, which I chaired, attempted to assess the potential of NMR in Biology and Medicine. The conclusions were cautious optimism with regard to imaging – at that point it was not clear what, if any, advantages it would have over CAT scans. In vivo NMR met with greater skepticism, because of the low sensitivity of the method, even though the enormous advantage of having a noninvasive method for chemical studies of intact organisms was obvious. History has since taught us that the caution concerning imaging was excessive, though understandable in an era in which distinguished radiologists were heard calling MRI “a solution in search of a problem" and refusing to devote any resources to it. On the other hand, the reservations about the usefulness of in vivo NMR have been largely borne out. Despite a massive amount of work over a 35 year period, beginning with the Nature paper by Hoult et al., [12], the approach has yielded little truly novel information, and its clinical applicability did not materialize. Its basic drawback – that what one would like to study one cannot see and what one can study is already well known by other methods – has so far not been overcome.

The following three conferences:

The seventh, organized by Ian C.P. Smith, J.P. Carver and Brian Sykes and held in St. Jovite, Quebec, Canada, September 19–24, 1976.
The eighth, organized by T. Miyazawa, S. Fujiwara and S .Ohnishi in Nara, Japan September 11–14, 1978.
The ninth, organized by Maurice Gueron, Patrick Cozzone and Philippe Devaux in Bendor, France September 11–6, 1980

are best characterized as progress report meetings in a mature field that had reached a plateau. The basic conceptual framework for biological applications of NMR was by then pretty much in place. There was no longer any serious question that the main difficulties of obtaining detailed structural information on biological macromolecules were technical and not inherent in the principles of the method. The inherent limitations of the method were largely known and clearly not an impediment to a far reaching success of the method. The questions that could be asked by the method were for the most part well defined. Yet, what is a matter of course now, had taken 20 years to establish.

There was a wealth of new results on new biochemical systems, although the questions asked and the methodological approaches used were all familiar from previous conferences. The dominant themes were the structure of enzyme and other protein binding sites and their complexes with small molecules, enzyme mechanisms by proton relaxation enhancement, the detection of conformational changes, heme iron proteins, the use of paramagnetic probes to obtain structural information and a revival of interest in using ions with large quadrupolar moments as probes of ion transport and catalytic mechanisms, the structure of oligonucleotides and the structure and dynamics of membranes and membrane models. At the meeting in St. Jovite work on membranes dominated the program, which was not surprising, given the interests of Ian Smith. Protein dynamics was a major topic at the Nara meeting. The detection of segmental flexibility in proteins was clearly demonstrated by the finding of a flexible segment in Tobacco Mosaic Virus and its identification by a comparison of mutants, as reported by K. Akasaka, K. Holmes and myself [13].

Among the most striking structural results of that period was the structure of the dinitrophenol (DNP) complex with a mouse antibody binding site presented by Raymond Dwek [14]. However, as all other NMR studies of binding sites it was still heavily dependent on crystallographic data both for assignments and for the definition of coordinates. Rather novel were the studies of the orientation, mobility and interactions of phospholipid headgroups in lipid bilayers by Joachim Seelig and his group. Also novel was the systematic investigation of tyrosine rotation in proteins by chemical shift anisotropy relaxation by Brian Sykes and his colleagues. The thorough and extensive studies of the structure and dynamics of the bovine pancreatic trypsin inhibitor (BPTI) by Kurt Wüthrich and his group, using two-dimensional methods previously developed by Aue and Ernst [15] and Jeener and coworkers [16] attracted considerable attention, especially the then still new versions, COSY and NOESY, to resolve coupling and NOEs rerspectively.

At the Bendor meeting one of the few remaining major issues was raised again. Many workers, especially those studying paramagnetic ion complexes of nucleotides and other small molecules were reporting structures and distances calculated on the assumption that these were rigid. It should be obvious to all, but it was not (and still is not always), that if the molecule is flexible, such distances and structures bear no relation to reality. The problem and its resolution were put in perspective in my 1980 paper “On the nature of Averaging" [17]. The points discussed there should

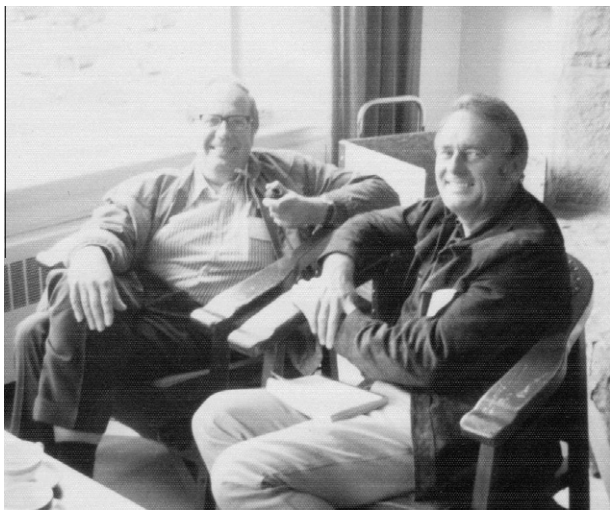

Fig. 2. Oleg Jardetzky and Robert Shulman at the seventh ICMRBS in St. Jovite, Quebec, Canada 1976. Oleg Jardetzky, Bob Shulman, and Mildred Cohn (Fig. 1) are recognized on the "Founders Medal", which is now a prestigious award given at each ICMRBS to a promising scientist in the field under the age of 41.

be understood by everyone using a spectroscopic method as a structural tool (see Fig. 2).

Meetings of that period are remembered not only for the high scientific quality of their content, but also for some amusing incidents. Time in St. Jovite was kept by using a traffic light and the program ran very smoothly until an eminent speaker, seeing the red light exclaimed "but I have just given my introduction!", and hid the traffic light under the table.

The Nara meeting (Fig. 3) was held shortly after the Biophysics Congress in Kyoto, which became famous for the scarcity of food. At the opening ceremony of the conference, Morton Bradbury as Chairman of the Council and the organizers entered the meeting hall to offer the customary welcoming speeches – only to find that no one would listen to them, because the entire audience rushed to the tables to get some food. One participant reaching for a sandwich, the last on the plate, by hand, was actually injured by another aiming for the same sandwich with a fork. There were no opening speeches.

At Bendor a behind the scenes war erupted between the organizers and some council members over the name of the conference. The French had announced it, using a fairly obvious abbreviation, as COMABIO. The question arose whether the name should be kept. The traditionalists, who did not want to change the name that has been in use for so long, prevailed. As someone who at the time argued for the traditionalists, I now regret that we did not have enough musical sense to change to an obviously much more beautiful name.

At Nara the decision had been made that the Council should select the site for a meeting 4 years hence, to allow more time for planning. Accordingly, Stanford, CA was chosen for the 10th conference in 1982, and at Goa for the 11th in 1984.

The 10th ICMRBS was held at Stanford University, CA August 28–September 3, 1982, organized by myself as chairman, A. Redfield and W.J. Orme-Johnson, and opened by Felix Bloch and Dominik Purpura, Dean of the Schol of Medicine. There were some 400 participants, not counting Stanford students and faculty who were allowed to attend individual sessions without registering.

This meeting marked – unintentionally – a major transition in the role of NMR in Biology and Medicine. For one, it was immediately preceded by the founding meeting of the Society of Magnetic Resonance in Medicine. The first plenary session was on imaging and in vivo NMR spectroscopy. Paul Lauterbur, Raymund Andrew and others presented some of the first and most beautiful images of the human body, especially the human head, which showed a remarkably fine resolution of soft issues, notably the brain. George Radda, Bob Schulman and several others presented results of both

Fig. 3. Group photograph of attendees at the eighth ICMRBS in Nara Japan 1978. Felix Bloch, who shared the 1952 Nobel Prize for "development of new ways and methods for nuclear magnetic precision measurements" is in the center of the front row, ninth from the left side.

^{31}P and ^{1}H spectroscopy of living matter. Among the most noteworthy reports were those of Justin Roberts from my laboratory on the first successful use of in vivo NMR for the study of plant metabolism and that of Patrick Cozzone on metabolic changes in perfused hearts in failure and in recovery. A satellite meeting and panel discussion on potential medical uses of magnetic resonance imaging and spectroscopy were held immediately following the main conference. Still it became obvious that the main audience for these developments was no longer the NMR community, but the medical community, notably the radiologists, most of whom were refusing to have anything to do with it just a couple years earlier.

The main part of the program was in the spirit and in the format of its predecessors – with progress reports on protein and nucleic acid structure, structure of complexes – all invariably partial structures, identifying a few of the residues involved, studies of enzyme mechanisms, at this time particularly of the relay at the catalytic site of serine proteases by John Markley and his group and W. Bachovchin and coworkers. There were many progress reports on the structure and dynamics of phospholipid membranes and membrane models, both by NMR and ESR, including a solid state NMR study by R.G. Griffin. Advances in our understanding of immunology and of metalloproteins, the uses of ESR and isotopes were all extensively discussed. A symposium was devoted to protein dynamics. G. Wagner reported a very thorough study of BPTI dynamics, using hydrogen exchabge, S. Opella presented a novel approach for the study of dynamics in very large structures using solid state NMR methods and several groups focussed on relaxation measurements. My own report on our model-free method of analysis of relaxation data and the possibility of solitons in proteins amounted to a very disappointing conclusion: A quantitative analysis of relaxation data was totally dependent on our preconceived notions. What was true then, remains true today – relaxation methods give reliable qualitative information on large differences in mobility, but contain no quantitative information that can be interpreted without major extraneous assumptions.

A foreboding of the second major transition in the field – the establishment of NMR as a method for protein structure determination – could be found in the lecture by Vladimir Bystrov, who by using a combination of COSY and NOESY methods and other measurements was able to obtain a complete set of assignments and the three dimensional structure of the bee venom toxin apamin, a 17 amino acid peptide. Similar structural studies of snake venom neurotoxins were also reported by the Japanese group of Tetsuo Miyazawa and structure determination of the icosipepide alamethicin using the same 2D metods, including SECSY, by Sunney Chan and his colleagues. Yet the extension of the method to peptides of higher molecular weight, which could qualify as small proteins was not reported until the 1984 meeting in Goa. There the 3D structure of the 47 residue lac repressor headpiece was reported by Zuiderweg, Kaptein and Wüthrich, and, independently by myself (both were published side-by-side in the Proceedings of the Conference on Bioorganic Chemistry in Alma-Ata, held a month earlier [18]. With this, often called the first NMR protein structure, the modern era of NMR in Molecular Biology had began.

Appendix A. Supplementary material

The supplementary data associated with this article consists of the complete program from the first ICMRBS meeting and can be found in the online version, at doi:10.1016/j.jmr.2010.07.005.

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